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## EFFECT OF CINCHOPHEN ON SECRETION OF CHOLIC ACID

I H ANNEGERS, M S, F E SNAPP, M S, A C IVY, PH D, M D, AND A J ATKINSON M D  
CHICAGO

Those investigators who have observed damage to the liver after administration of cinchophen to laboratory animals used doses at least ten times the equivalent dose for human beings estimated on the basis of body weight.<sup>1</sup> Those who have used the same or smaller doses failed to find any striking evidence of hepatic damage<sup>2</sup> or of depression of hepatic function.<sup>3</sup> Stalker, Bollman and Mann<sup>4</sup> gave twice the average human dose to a relatively large number of dogs for periods up to thirty-nine weeks. Though they observed gastrointestinal intolerance, which usually subsided, they did not observe jaundice or microscopic evidence of pathologic changes in the liver and other tissues, other than "peptic ulcer."

From the Department of Physiology, Northwestern University Medical School

Aided in part by grants from the Dawes-Atkinson and the Marjorie E Newman Fund

1 (a) Churchill, T P, and Van Wagoner, F H. Cinchophen Poisoning, *Proc Soc Exper Biol & Med* **28** 581, 1930. (b) Knoble, R M, and Smith, H A. The Effect of Cinchophen on the Liver of White Rats, *Am J Physiol* **97** 537, 1931. (c) Barbour, H G, and Fisk, M E. Liver Damage in Dogs and Rats After Repeated Oral Administration of Cinchophen, *J Pharmacol & Exper Therap* **48** 341, 1933. (d) Lehman, A J, and Hanzlik, P J. Cinchophen Toxicosis, *Arch Int Med* **52** 471 (Sept) 1933. (e) Radwin, L S, and Lederer, M. Effect of Cinchophen on the Albino Rat, *Arch Path* **15** 490 (April) 1933.

2 (a) Reichle, H S. Cinchophen Poisoning. An Attempt to Produce Toxic Cirrhosis of the Liver in Rats, *Arch Int Med* **49** 215 (Feb) 1932. (b) Barbour, H G, and Gilman, A. Cinchophen and Tolysin. Comparison of Effects of Administration of Each in Rats, *J Pharmacol & Exper Therap* **55** 400, 1935. (c) Berman, A L, Sharp, E, Atkinson, A J, and Ivy, A C. Effect of Cinchophen on Bile Formation, *J Lab & Clin Med* **28** 682, 1943.

3 Furth, O, and Scholl, R. Biochemical Studies on Mechanism of Phenylcinchoninic Intoxication, *J Lab & Clin Med* **18** 991, 1933. Myers, H B, and Goodman, L. Cinchophen Hepatitis, *Arch Int Med* **49** 946 (June) 1932. Churchill and Van Wagoner.<sup>1a</sup> Lehman and Hanzlik.<sup>1d</sup>

4 Stalker, L K, Bollman, J L, and Mann, F C. Effect of Cinchophen on the Liver and Other Tissues of the Dog, *Proc Soc Exper Biol & Med* **35** 158, 1936.

It was believed that if cinchophen has a direct toxic effect on the liver it should be manifested by a disturbance of secretion of cholic acid since the output of that substance is readily affected by an infectious or toxic hepatitis. In a previous publication we<sup>2c</sup> failed to observe any significant decrease in secretion of cholic acid when 1 Gm of the drug was given by mouth daily for three days up to thirty days. However, in all but 1 of the experiments the bile drained to the outside into a bag and from 60 to 75 per cent of the orally administered cinchophen was recovered in the bile in the bag. It was thought that if the administered cinchophen was permitted to undergo continuous enterohepatic circulation evidence of disturbance of secretion of cholic acid might result.

### METHODS

*The Preparation of the Animals*—Dogs weighing from 10 to 12 Kg were prepared with chronic biliary fistulas by the method of Kocour and Ivy.<sup>5</sup> A small tube was inserted into the duodenum which led to the outside of the dog through a stab wound in the abdomen for the return of bile to the dog's intestine. Thus the bile could be collected hourly, and a small sample (0.1 cc) could be withheld for estimation of cholic acid<sup>6</sup> and the remainder returned to the duodenum.

All the animals had been operated on at least one month previously and had been maintained on a standard diet from that time to the beginning of these experiments. Previous to, and during experiments, the daily ration was divided into three portions and fed every eight hours.

*The Dose of Cinchophen*—The dose of the drug employed in treatment of gout ranges from 7.5 to 30 grains (0.5 to 2 Gm) daily, or from 7 to 28 mg per kilogram of body weight for a patient weighing 70 Kg.<sup>14</sup> A dose of 7.5 grains (0.5 Gm) three or four times daily for three consecutive days each week is the dose most recently recommended.<sup>7</sup> Some use 45

5 Kocour, E J, and Ivy, A C. The Effect of Certain Foods on Bile Volume Output in the Dog by a Quantitative Method, *Am J Physiol* **122** 325, 1938.

6 Reinhold, J G, and Wilson, D S. The Determination of Cholic Acid in Bile, *J Biol Chem* **96** 637, 1932.

7 Hench, P S. Diagnosis and Treatment of Gout and Gouty Arthritis, *J A M A* **116** 453 (Feb 8) 1941.

grains (3 Gm) daily, which is 42 mg per kilogram for a patient weighing 70 Kg.<sup>8</sup> In order to be more certain of obtaining effects from the drug, we chose to give from 50 to 100 mg per kilogram of body weight daily.

The cinchophen used was snow white, free of the odor of phenolquinoline and completely soluble in alkaline aqueous solution (Calco Company). It was a purer product than the cinchophen on the market and was used by us several years ago in other experimental work.<sup>9</sup>

*The Plan of the Experiments*—I The animals were placed on the standard diet and fed every eight hours without return of bile. This was to obtain control data regarding their basal synthesis of cholic acid so that the effect of cinchophen on it could be determined.<sup>2c</sup> II Then bile was returned hourly without any change in feeding. This procedure was to obtain control data to compare with the observations made with the same regimen plus administration of cinchophen. III Procedure II was then repeated with admin-

TABLE 1—Data Showing Slight Effect of 0.5 Gm of Cinchophen (T1) Every Twelve Hours and 0.25 Gm Every Six Hours (T2) on Secretion of Cholic Acid<sup>\*</sup>  
Dog A3

Hours †	Volume of Bile in Cc ‡			Cholic Acid Output in Mg		
	C	T1	T2	C	T1	T2
6	50	64	71	631	768	1,713
12	70	94	120	1,734	2,174	2,411
18	92	124	123	2,621	2,362	3,610
24	77	126	112	2,141	2,994	3,533
30	107	154	139	2,962	2,894	3,771
36	119	131	175	3,743	4,634	4,269
42	127	143	162	4,300	4,121	3,815
48	130	104	175	4,350	2,043	5,102
Total	762	830	1,032	23,482	21,990	28,279
48-60	65	90	90	673	Trace	1,265

\* Except during the last six hours of test 1.

† The hourly outputs of volume and cholic acid are added to give the six hour total.

‡ This dog is unusual in the large amount of cholic acid synthesized and secreted. C, control, bile returned hourly without drug, T1, 0.5 Gm of cinchophen given every twelve hours, T2, 0.25 Gm of cinchophen given every six hours.

istration of cinchophen. IV Finally, the administration of cinchophen and the return of bile were stopped and the cholic acid synthesis with the diet alone was again determined during the next three or four days. These data were obtained to supply information showing whether cinchophen had disturbed the cholic acid-synthesizing mechanism of the liver.

## RESULTS

Sixteen experiments were performed on 8 dogs.

Since the animals responded differently at different times, the results for each animal will be summarized. Because it is impractical to submit all of the hourly data, only portions will be shown and the remainder will be condensed as averages.

8 New and Nonofficial Remedies, Chicago, American Medical Association Press, 1941.

9 Reid, P. E., and Ivy, A. C. Gastric Mucin a Prophylactic Against Gastro-Intestinal Ulcers and "Acute" Toxicity Resulting from Cinchophen, *Proc Soc Exper Biol & Med* 34:142, 1936.

Dog 1 (A3)—When 0.5 Gm of the drug was given every twelve hours (test 1, table 1), the secretion of cholic acid was not affected until six hours after the third dose. The effect increased so that during the first six hours after completion of the hourly return the bile contained only traces of cholic acid. It should be noted that a part of the forty-eight hour meal was refused. Appetite and output of cholic acid then returned to normal. On referring to column 4, table 4, it will be seen that basal synthesis of cholic acid was not disturbed after the animal recovered from the twelve hours of depression of secretion of cholic acid. The dose of 0.25 Gm every six hours (table 1, test 2), given one week after the first experiment, did not depress the output of cholic acid or affect the gastrointestinal tract as judged by objective symptoms. In fact, it would appear that the output of cholic acid was increased above the control level, the forty-eight hour output being 20 per cent above the forty-eight hour control value.

Dog 2 (B3)—This animal after receiving the first dose of 0.5 Gm of the drug manifested the usual increment in output of cholic acid which follows hourly return of bile. However, at eighteen hours the output decreased, and just prior to twenty-four hours vomiting and diarrhea occurred. The animal refused food thereafter. Administration of the drug was continued, however, until four doses had been given, and the bile was returned hourly. The output of cholic acid was low, and only traces were present during the thirty-eighth and thirty-ninth hours. When return of bile was stopped, the output of cholic acid was so low that it could not be accurately estimated, which shows that the animal did not synthesize cholic acid and did not excrete the cholic acid absorbed from the intestine. Diarrhea had disappeared. The animal continued to refuse food, though the liver recovered sufficiently to synthesize that amount of cholic acid which occurs during fasting in a healthy fistula dog. The animal died the fifth day after the experiment, and autopsy revealed only gastroenteritis.

This observation indicates that it is hazardous to continue administration of cinchophen after manifestation of the symptoms of gastrointestinal irritation.

Dog 3 (D6)—Four tests were performed on this animal (table 2). In the first test, in which a dose of 0.5 Gm every twelve hours was used, the output of cholic acid was depressed during the first sixteen hours, again during the twenty-first and twenty-second hours, and again during the twenty-ninth and fortieth hours. The output of cholic acid for the entire period with cinchophen was 37 per cent less than that for the control period. Synthesis of cholic acid was not affected during the post-treatment basal period following this test (table 4).

During the second test, one week later, the same dose of cinchophen was used with 1 Gm of calcium gluconate. The output of cholic acid during the test was 13 per cent less than the control value, though a definite depression occurred at no time during the test. The post-treatment basal synthesis of cholic acid was within the normal range.

In the third test, several weeks after the second, 0.25 Gm of the drug was given every twelve hours. The output of cholic acid during the period was 9 per cent above the control level.

In the fourth test, performed several weeks after the third, 1 Gm of the drug was given every twenty-four hours for two days, 2 Gm of calcium gluconate being given with the second dose of the drug in an

effort to observe a difference in cholic acid response when the calcium was given. The output of cholic acid was greater than the control value throughout the forty-eight hour period, and the total output was 25 per cent greater. The post-treatment synthesis of cholic acid was about the normal value for basal conditions with diet alone (table 4).

Dog 4 (C4)—This animal received cinchophen on three occasions. The output of cholic acid was depressed for two hours after the first dose of cinchophen (0.5 Gm every twelve hours). After that the output remained

out sodium bicarbonate. No depression of output or synthesis of cholic acid during this test or during the post-treatment period occurred.

Dog 5 (D7)—Two tests were performed on this animal, one with the 0.5 Gm dose and one with a 0.25 Gm dose every twelve hours. With the 0.5 Gm dose no depression of output of the cholic acid occurred at any time, in fact, 18 per cent more cholic acid was secreted during the forty-eight hour test period than during the forty-eight hour control period. Several weeks later with the 0.25 Gm dose a depression occurred

TABLE 2—Results of Four Tests on the Same Dog  
Dog D6

Hour *	Volume in Cc †					Cholic Acid in Mg				
	O	T1	T2	T3	T4	O	T1	T2	T3	T4
6	24	44	52	40	27	183	Trace	351	333	231
12	44	60	88	71	47	457	169	762	836	610
18	49	87	80	90	82	743	309	677	1,154	1,152
24	60	73	75	78	110	1,185	577	861	1,323	1,409
30	60	75	65	66	123	1,142	795	1,072	1,090	1,540
36	64	92	107	82	95	1,055	976	843	1,246	1,638
42	55	105	103	72	118	971	919	1,052	1,181	1,470
48	74	89	81	62	116	1,711	927	852	987	1,258
Total	420	625	654	561	719	7,447	4,672	6,470	8,150	9,308
54 ‡	37	28	48	34	60	830	391	478	599	495
60	29	31	35	25	37	320	Trace	152	250	152
72	28	61	59	64	62	256	587	320		279
Total	514	745	796	684	878	8,853	5,600	7,420		10,234

\* Hourly outputs of volume and cholic acid are added to give six hour values.

† O, control, bile returned hourly without drug, T1, 0.5 Gm of cinchophen every twelve hours, T2, 0.5 Gm of cinchophen every twelve hours plus 1 Gm of calcium gluconate, T3, 0.25 Gm of cinchophen every twelve hours, T4, 1.0 Gm of cinchophen every twenty four hours.

‡ Hourly return of bile stopped at forty eight hours.

TABLE 3—Output of Cholic Acid During the First Twelve Hours of the Control and After the First Dose of Cinchophen with Hourly Return of Bile \*

Mg Cholic Acid †											
	Dog A3		Dog B3	Dog C4		Dog D7		Dog D4		Dog D6	
Hour	O	T1	T1	O	T2 ‡	O	T2 ‡	O	T1	O	T1
1	45	43	77	8	Trace	10	70	6	Trace	10	4
2	87	110	120	15	Trace	25	44	22	Trace	21	Trace
3	121	110	86	25	Trace	34	Trace	43	4	35	Trace
4	132	131	71	8	Trace	28	59	26	12	35	Trace
5	182	166	86	34	Trace	65	103	54	7	43	Trace
6	84	231	100	22	34	41	130	72	6	41	Trace
7	344	202	144	34	Trace	34	130	108	Trace	58	Trace
8	195	259	264	105	31	86	Trace	77	13	83	Trace
9	336	344	373	95	Trace	28	Trace	39	31	10	Trace
10	313	483	390	136	Trace	105	Trace	73	47	95	Trace
11	168	529	344	156	Trace	63	141	73	57	92	94
12	328	357	305	165	Trace	88	72	81	39	119	75
Total	2,365	2,942	2,360	803	116	607	749	674	216	1,169	169

\* Only those dogs that were affected by the cinchophen are listed. The marked depression in dogs A3 and B3 was not manifested the first twelve hours. No control was made on B3.

† O, control, bile returned hourly without drug, T1, first test of dog with cinchophen, T2, second test with cinchophen. A3, B3, C4 and D6 received 0.5 Gm of cinchophen every twelve hours, D4 and D7 received 0.25 Gm of cinchophen every twelve hours.

‡ One gram of sodium bicarbonate was given with the cinchophen.

at or slightly above the control level (table 4), the same was true for basal synthesis of cholic acid with the diet, after administration of cinchophen was stopped.

Two weeks later the first dose of cinchophen was repeated, except that 1 Gm of sodium bicarbonate was given with each dose. The output of cholic acid was markedly depressed (table 3) for the first twelve hours and in the twenty-eighth hour of the test. During the last twelve hours of the forty-eight hour period, the output was so markedly increased that the total for the forty-eight hour period was only 14 per cent below the control value (table 4). Synthesis during the post-treatment period was not influenced (table 4).

Six weeks after the first test, the same procedure was repeated with the same dose of cinchophen with-

during the third hour and from the eighth to the eleventh hour after the first dose (table 3). This depression, however, was more than compensated for later in the test period, since the total output of cholic acid for the test was 12 per cent above the control value. The post-treatment basal synthesis of cholic acid was not affected in either test.

It is interesting to note that this animal was affected more by a dose of 250 mg of the drug than by 500 mg and that depression occurred the second time the animal was subjected to the influence of cinchophen but not the first time.

Dog 6 (D4)—This animal first received a dose of 0.25 Gm of cinchophen and two weeks later a dose of 0.5 Gm every twelve hours.

During the first test the output of cholic acid was depressed during the first fourteen hours (table 3), later recovery occurred, so that the total decrease in output for the period was 28 per cent. During the post-treatment period, basal synthesis of cholic acid with the diet alone was greater than during a control period under similar conditions.

During the second test, with 0.5 Gm of cinchophen, the output of cholic acid was not depressed at any time, during the test with the drug 48 per cent more cholic acid was secreted than during the control test (table 4).

Dog 7 (D8)—One experiment was performed in which 250 mg of cinchophen was given the twelfth hour and 500 mg the twenty-fourth hour of return of bile. The output of cholic acid was not depressed after the drug was given or in the post-treatment period.

Dog 8 (E6)—One experiment was done, in which 125 mg of cinchophen was given the twelfth, twenty-fourth

or 25 per cent. It is important to realize that if hourly analyses for cholic acid had not been made, depression of the output would have been discovered in only 4 tests. In 1 dog depression of secretion of cholic acid occurred during the second administration of cinchophen and not during the first test with the drug (C4, table 4).

Anorexia occurred in only 2 instances. In 1 (A3, test 1) it was probably in part responsible for the late decrease in output of cholic acid since formation of cholic acid probably depends on metabolism of protein. In the other case the animal manifested vomiting and diarrhea after the second dose of cinchophen and refused all food until death occurred the fifth day after the completion of the forty-eight hour test. This

TABLE 4—Summary of Results

Dog	A Cholic Acid Basal on Diet Alone * Range in Mg	I Predrug Cholic Acid Basal Control in Mg	II Control Bile Returned Hourly No Drug (Mg)	III Test as II with Drug (Mg)	Per Cent of Change Referred to II	IV Postdrug Cholic Acid (Compare with A and I [Mg])	Dose of Drug
A3	1,400-2,000 (10 tests)	1,437 1,675	23,482 23,482	21,990 29,279	-6 +20	1,613 1,722	0.5 Gm b i d 0.25 Gm q i d
B4†		1,547		5,664		910†	0.5 Gm b i d
C4	980-1,700 (6 tests)	985 1,567 1,515	9,145 9,145 9,145	10,026 7,876 9,918	+9 +14 +8	1,243 1,010 1,412	0.5 Gm b i d 0.5 Gm b i d 0.5 Gm b i d
D7	1,100-2,400 (4 tests)	2,360 1,090	6,071 6,071	8,664 7,181	+18 +12	2,710 1,560	0.5 Gm b i d 0.25 Gm b i d
D4	1,400-1,800 (3 tests)	2,000 1,704	5,757 7,757	4,158 8,548	-28 +48	2,500	0.25 Gm b i d 0.5 Gm b i d
D6	900-1,400 (4 tests)	1,013 1,312 950 773	7,447 7,447 7,447 7,447	4,672 6,470 8,150 9,308	-37 -13 +9 +25	950 1,252 1,070 762	0.5 Gm b i d 0.5 Gm b i d 0.25 Gm b i d 1.0 Gm every 24 hours ‡
D8	1,824 (4 tests)	1,950		20,599		1,865	0.750 Gm b i d
E6	1,650 (3 tests)	1,335		15,946		1,332	0.125 Gm b i d

\* Each test is the average of 3 days' basal output on diet alone.

† This animal refused food during this test and hence the output represents the fasting synthesis of cholic acid. The animal died as a result of the test; no other tests were made previous to this one.

‡ 1.0 Gm sodium bicarbonate was given with the drug.

§ 1.0 Gm of calcium gluconate was given with each dose of the drug.

and thirty-sixth hours of return of bile. The output of cholic acid was not depressed after administration of the drug was started. There was no post-treatment depression of the output under basal conditions with the diet alone.

#### COMMENT

A temporary depression in output of cholic acid was observed in six out of the 8 dogs in this study. Depression occurred with doses of 0.25 Gm every twelve hours as well as with 0.5 Gm every twelve hours. In the 16 tests on 8 dogs, definite depression occurred at some time during the forty-eight hour period of administration of the drug and hourly return of bile in 6, or 38 per cent, of the tests. In 4 of these 6 tests depression occurred chiefly after the first dose of the drug. In 1 test depression occurred only after the third dose, and in the other it occurred after two doses. The depression was sufficiently great or prolonged to influence the total forty-eight hour output in only 4 tests,

shows that a definite disturbance of appetite although a good indication that the liver is affected to the extent that a decrease in output of cholic acid occurs, is not an entirely reliable criterion. Except for analysis of the bile for cholic acid, it is the best criterion that we have observed in these 8 animals and in 10 others which we have studied but which are not mentioned in this report because an hourly enterohepatic circulation of bile and cinchophen was not established.

In 2 and possibly 3 tests (dogs A3, D4 and D6, table 4), the output of cholic acid was increased with administration of cinchophen. We cannot be certain of this, however, since the hourly return of bile during a forty-eight hour period leads to a more rapid accumulation of cholic acid in the enterohepatic circuit at some times than at other times in the same dog. That this irregularity of accumulation of cholic acid



does not explain the depression seen in 6 dogs is apparent from the tables. The output of cholic acid was almost completely suppressed for periods of several hours with cinchophen, which differs from the more steady and less marked depression which may appear to occur in some of a series of tests on any single dog. Observations made in other work<sup>10</sup> show that the rate of accumulation of cholic acid in the enterohepatic circuit may vary as much as 15 per cent from test to test in the same animal. Hence, we doubt the significance of any increase smaller than 20 per cent under the conditions of these experiments.

We were especially interested in ascertaining whether forty-eight hours of administration of cinchophen would affect the liver in relation to synthesis of cholic acid from the protein in the diet. The data (table 4, column 4) reveal that in the period from twenty-four to seventy-two hours after the termination of the administration of the drug, synthesis of cholic acid was not significantly altered. In 3 instances the output of cholic acid was depressed when return of bile and administration of cinchophen were stopped at the end of forty-eight hours for from two to twelve hours, but the return to the normal level was prompt thereafter. In 1 of these tests, on B3, the animal that died, the synthesis which occurred after the marked depression due to the drug was a high normal value for fasting. Synthesis occurred even up to the hour of death. The sample of bile in the collecting cylinder when the animal died contained a normal amount of cholic acid for the fasting condition.

Recovery of synthesis and output of cholic acid after administration of the drug has been discontinued might be anticipated, since in a subsequent study it will be shown that the bile becomes free of cinchophen in fifteen to twenty-four hours after administration of the last of a series of doses from 0.250 Gm up to 1 Gm daily with return of the bile to the intestine hourly. However, recovery of output of cholic acid will occur (tables 3 and 4) after it has been initially depressed by cinchophen even while the administration of the drug is continued. This fact, together with the fact that dog B3 died when the liver had been free of exposure to cinchophen for five days, indicates that the drug may in some instances injure some vital function of the liver unrelated to the synthesis and excretion of cholic acid.

On the contrary, it may be argued that gastroenteritis was the cause of death of dog B3 and not hepatic damage due to the cinchophen. It may also be argued that the suppression of secretion of cholic acid observed for short periods on some occasions in dogs other than B3 was due to a disturbance of digestion and absorption of protein. Since we did not analyze the stools for nitrogen, this possibility cannot be answered by submission of direct evidence. However, as is well known, the liver of the fasting dog synthesizes and secretes cholic acid, and it is difficult to believe that cinchophen would so alter the intestine that none or only traces of the cholic acid in the bile initially returned to the intestine would be absorbed. So we attribute the marked depression in secretion of cholic acid, when observed, to an effect of the cinchophen on the hepatic cells.

In the 3 tests in which sodium bicarbonate or calcium gluconate was given with the cinchophen, the volume output or cholic acid content of the bile was not modified significantly. In test 2 on dog C4, in which sodium bicarbonate was given, cinchophen initially depressed the output of cholic acid (table 3). This evidence supports the view that the suppression of secretion of cholic acid, when it occurs, is not due solely to gastrointestinal irritation.<sup>11</sup>

#### SUMMARY AND CONCLUSIONS

Doses of cinchophen which on the basis of body weight are from one to four times the dose recently suggested for the use in the management of gout in human beings<sup>7</sup> and which in the past have failed to cause disturbance in hepatic liver function as studied by the ordinary tests<sup>10</sup> may sometimes cause a marked temporary depression of synthesis and secretion of cholic acid by the livers of dogs. After such doses of cinchophen a complete temporary suppression of secretion of cholic acid may occur in the absence of anorexia and objective gastrointestinal symptoms.

Most animals recover from the suppression of synthesis and secretion of cholic acid during repeated administration of cinchophen in the doses used.

Since 1 extremely susceptible animal in our series recovered from the suppression of synthesis and secretion of cholic acid and regardless

<sup>10</sup> Berman, A. L., Snapp, E., Ivy, A. C., and Atkinson, A. J. On the Regulation and Homeostasis of the Cholic Acid Output in Biliary Fistula Dogs, *Am J Physiol* **131** 776, 1941.

<sup>11</sup> Schnedorf, J. G., Bradley, W. B., and Ivy, A. C. Effect of Acetylsalicylic Acid upon Gastric Activity and the Modifying Action of Calcium Gluconate and Sodium Bicarbonate, *Am J Digest Dis & Nutrition* **3** 239, 1936. Reid and Ivy.<sup>9</sup>



of this died within a week, it is concluded that death after administration of cinchophen is due to some vital function of the liver unrelated to the synthesis and excretion of cholic acid or to some general toxic effect not confined to the liver

Since synthesis and secretion of cholic acid occur in the fasting animal, since cholic acid introduced into the intestine was not secreted in the bile during various hourly periods of cinchophen medication in animals that were susceptible to the drug and since secretion of cholic acid may be completely suppressed temporarily without anorexia or other signs of gastrointestinal upset, it is concluded that the suppression of synthesis and secretion of cholic acid is due chiefly to the effect of the drug on

the liver and not to its effect on the gastrointestinal tract. However, in the absence of an analysis of the bile for cholic acid, anorexia is the first and most reliable indication of sufficient damage to the liver to cause a failure of synthesis and secretion of cholic acid

On the basis of the criterion of depression of secretion of cholic acid, susceptibility to the drug varies in the same and in different animals. This variation observed in a selected group of animals with biliary fistulas in this laboratory was more fully discussed in a previous paper<sup>12</sup>

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12 Annegers, J. H., Snapp, F. E., Atkinson, A. J., and Ivy, A. C. Variations in Susceptibility to Cinchophen as Observed in Animals with Bile Fistulas, *J. Lab. & Clin. Med.* 28:828, 1943

# THE MORGAGNI-STEWART-MOREL SYNDROME

REPORT OF A CASE WITH PNEUMOENCEPHALOGRAPHIC FINDINGS ~

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The symptom complex of hyperostosis frontalis interna, or its variants described by Sherwood Moore,<sup>1</sup> with associated endocrine and neuropsychiatric manifestations, had stimulated a degree of interest, as evidenced by the increasing literature on the subject, to warrant the report of cases which may throw more light on the etiologic background of this interesting condition. The triad of hyperostosis frontalis interna, obesity and virilism had been described originally by Morgagni<sup>2</sup> in 1765. Much later (1928) the appearance of a more careful study, by Stewart,<sup>3</sup> in which he described the autopsy observations and added the clinical feature of a psychosis to the syndrome, and the first description of the syndrome as observed in a living person, by Morel<sup>4</sup> in 1930, brought the group picture of calvarial hyperostosis and endocrine, metabolic and neuropsychiatric manifestations into clearer relief as an entity. Moore's elaborate work in reexamining roentgenograms of numerous human skulls revealed that among 6,650 specimens four types of calvarial hyperostosis could be distinguished, their frequency in order of appearance being hyperostosis frontalis interna 1.44 per cent, nebula frontalis 1.14 per cent, hyperostosis calvariae diffusa 0.6 per cent and hyperostosis frontoparietalis 0.3 per cent. He defined a symptom complex which later he termed "metabolic craniopathy."<sup>5</sup> A complete review of the literature and of the hypotheses regarding the causation and the descriptions of

the pathologic changes are not the purpose of this paper and may be consulted in the excellent reviews by Knies and Le Fever,<sup>5</sup> Perkins and Biglan<sup>6</sup> and Andrews.<sup>7</sup> The entire syndrome has been broadened to include both the original concept of Morgagni and those of Stewart and Morel and the signs and symptoms described by subsequent authors. In the main, the syndrome consists of the following elements: one of the types of calvarial hyperostosis as described by Moore, endocrine and metabolic disturbances, such as obesity, virilism and menstrual disorders in female patients and gonadal deficiency in male patients, hypertension, and neuropsychiatric manifestations, such as headaches, cranial nerve defects (disturbance in olfaction, seventh nerve palsy, diplopia, amblyopia), fatigability, muscular weakness, narcolepsy, convulsive seizures, incoordination, dizziness, staggering gait, attacks of sweating, disturbances of speech, mental dulness, defects of memory, changes in personality, irritability, mental deterioration and, terminally, dementia. It is not essential, however, that all of these manifestations, with the exception of the pathognomonic roentgen finding of hyperostosis interna, be found in an individual case. Briefly, the cause, although by no means definitely established, appears to be of both metabolic and endocrine origin,<sup>8</sup> concerned

\* From the Doctors Hospital

|| From the University of Pennsylvania, Graduate School of Medicine

1 Moore, S. (a) Hyperostosis Frontalis Interna, Surg, Gynec & Obst **61** 345-362, 1935, (b) Calvarial Hyperostosis and the Accompanying Symptom Complex, Arch Neurol & Psychiat **35** 975-981 (May) 1936, (c) Metabolic Craniopathy, Am J Roentgenol **35** 30-39, 1936

2 Morgagni, J. B. De sedibus et causis morborum per anatomen indagatis libri quinque, ed 2, Padua, sumpt Pemonini, 1765, book 2, epistle 27

3 Stewart, R. M. Localized Cranial Hyperostosis in the Insane, J Neurol & Psychopath **8** 321-331, 1928

4 Morel, F. L'hyperostose frontale interne. Syndrome de l'hyperostose frontale interne avec adipose et troubles cerebraux, Paris, Gaston Doin & Cie, 1930

5 Knies, P. T., and Le Fever, H. E. Metabolic Craniopathy. Hyperostosis Frontalis Interna, Ann Int Med **14** 1858-1888, 1941

6 Perkins, O. C., and Biglan, A. M. Hyperostosis Frontalis Interna. A Review of the Literature, Psychiatric Quart **12** 340-350, 1938

7 Andrews, C. T. Hyperostosis Frontalis Interna, Brit M J **2** 185-187, 1942

8 (a) Mortimer, H. Influence of Anterior Pituitary on Cranial Form and Structure, A Research Nerv & Ment Dis, Proc (1936) **17** 222-238, 1938, (b) in discussion on Carr,<sup>8a</sup> p 986 (c) Mortimer, H., Levene, G., and Rowe, A. W. Cranial Dysplasias of Pituitary Origin, Radiology **29** 135-157 and 279-290, 1937 (d) Carr, A. D. Neuropsychiatric Syndromes Associated with Hyperostosis Frontalis Interna, Arch Neurol & Psychiat **35** 982-989 (May) 1936 (e) Henschen, F. Hyperostosis verrucosa frontalis interna und deren Bedeutung, Acta path et microbiol Scandinav, 1936, supp 26, pp 95-97, (f) Le "syndrome de Morgagni" (hyperostose frontale interne, virilisme, adipose), Ann d'anat path **13** 943-960, 1936, (g)

(Footnotes continued on next page)

chiefly with fat and calcium derangement and dysfunction of the anterior lobe of the pituitary and the parathyroid, thyroid and adrenal glands. It is the consensus among most observers that this syndrome occurs almost exclusively in the female, Moore<sup>1b</sup> reporting a 98 per cent incidence, and is seen mainly in late adult life.

It will be seen from the symptoms enumerated and will be illustrated in the following case report that this syndrome may be readily confused with other endocrine or neuropsychiatric disorders, especially psychoneuroses, dementia paralytica, multiple sclerosis and tumor of the brain.<sup>9</sup> It is important, therefore, not to fall into the error either of minimizing the significance of the symptoms, thereby escaping the diagnosis, or of treating the patient "for something which he does not have."<sup>1b</sup>

The following case is reported to illustrate failure to recognize the condition over a period of many years because of the slow, progressive and apparently innocuous nature of the disease which was euphemistically dismissed as a harmless psychoneurosis, and because of the pneumoencephalographic findings, which may yield some information affording a better understanding of the neuropsychiatric aspects of the syndrome. Only one report of pneumoencephalographic findings has appeared thus far in the literature, Kries and Le Fever<sup>5</sup> reported plastic arachnoiditis in one case (case 20) and dilatation of the anterior horns of the lateral ventricles in another (case 24).

#### REPORT OF CASE

A G, a married woman aged 39, was admitted to the neurologic service of the Doctors Hospital, on Nov 20, 1942, giving as chief complaints headaches and attacks of drowsiness accompanied with convulsive seizures. Her family physician had made the diagnosis of a psychoneurosis.

Both parents were dead, the father died in an accident at 36 years of age, her mother died of pneumonia at 59 years of age. Three siblings were living and well. There was no history of tuberculosis, cancer, diabetes, cardiorrenal disease, epilepsy or mental disease in the immediate or collateral members of the family. At the age of 8 years she had a minor injury of the head. The menses began when she was 11 years old and occurred at irregular intervals. Since the birth of

a son, her only child, 12 years prior to her admission to the hospital, her periods had been regular but the flow scanty.

Her presenting complaints, drowsiness and "shaking spells," had occurred frequently during the three months prior to admission. These spells usually came on about one hour or so after meals, often manifesting themselves in an abortive form by discomfort and inability to concentrate. Although vague about the time of inception of her present illness, she believed it began about ten years previously, with buzzing in the head. Six years previously she experienced "violent blood rushes to the head," which on the following day were succeeded by headache and profuse sweating. This endured for one year. Drowsiness made its appearance about five years before her admission, and accompanying this was an impairment of memory. Moreover visual disturbances, consisting of "haze" over her eyes and a sensation of "sand in her eyes," together with double vision, came on about this time. The double vision, although still present at times, had receded considerably. She had consulted numerous ophthalmologists and finally, by a process of self-taught "ocular exercise," had found improvement. During the past year, having been employed as a telegrapher she had noted that she would omit syllables or whole words and occasionally transpose words. For the past few years she had slept poorly, and recently she had experienced a sensation as though some one were under her bed pulling the bedclothes off and at times pushing her feet up. For three or four years past she had had bouts of "grogginess" and staggering gait, often being taken for a "drunk." Recently, during these periods of uncertain gait she had suffered from clumsiness with her hands so that she often dropped objects. Moreover, she had been told that at such times she took on a peculiar expression with a livid color to the skin and that her eyelids drooped. The "shaking spells," although present for a longer time, had occurred at frequent intervals during the past six months. These appeared at any time during the day or night, and she did not recall the duration of each seizure. Headache had been present for six months. The pain involved mainly the left side, but occasionally it was initiated over the forehead and involved the right side as well. She had not been able to work during the past six months because of the many symptoms besetting her. The numerous physicians whom she had consulted usually put her off with the statement "go home and forget about it, you're just trying to get sympathy for yourself."

The patient was a fairly well developed woman. During the period of observation in the hospital she was given to swings of mood, at some times being euphoric and at others moody and depressed. During her elated phases she was extremely garrulous and discussed her many symptoms with a degree of relish. Occasionally she would stop abruptly while speaking and state that she had completely forgotten what she had intended saying. She was abrupt in manner and suspicious and believed that her period of observation in the hospital constituted making her a "guinea-pig." She was properly oriented for time, place and person, but at times, after giving correct replies, she would say that she did not know who she was or where she was. Memory for recent events was not impaired, but she was evasive when being tested for remote events. There was some impairment of immediate recall. She showed no hallucinatory or delusional trends while in the hos-

Morgagni Syndrome, Hygiea 48 65-85, 1936, (h) Morgagnis Syndrom Hyperostosis frontalis interna, Virilismus, Obesitas, in Aschoff, L., Cullen, W., Koch, W., and Schurmann, P. Veröffentlichungen aus der Konstitutions- und Wehrpathologie, 1937, Berlin, Gustav Fischer, vol 9, pp 1-82 (i) Grieg, D M. On Intracranial Osteophytes, Edinburgh M J 35 165-191 and 237-260, 1928 (j) Dressler, L. Ueber die Hyperostosen des Stirnbens, Beitr z path Anat u z allg Path 78 332-363, 1927

9 Kries and Le Fever<sup>5</sup> Carr<sup>1a</sup> Schwab, S I, in discussion on Carr,<sup>8d</sup> p 985

pital Throughout her stay of twenty-two days she continuously questioned the need for studies She would remain in bed for several days in a surly, negativistic mood, followed by a period of considerable activity



Fig 1—Note the generalized thickening and increased density of the skull (which prevented proper penetration of the x-rays) with marked hyperostosis frontoparietalis interna

during which she would walk up and down the hospital corridors

The contour of the skull was normal There was no defect in olfaction Vision was intact, and the fields



Fig 2—Posteroanterior view The hyperostosis interna is marked just lateral to the vertex The calcification in the falx measures 4 mm by 2 cm

were full The ophthalmoscopic examination showed a general hyperemia of the disks and retinas The vessels were full, especially the veins, which were broader than normal The left eye was larger and somewhat

proptosed, producing the appearance of a left external strabismus The pupils were round, regular and equal and responded promptly to light and in accommodation The extraocular movements were well performed in all directions Diplopia and nystagmus could not be



Fig 3—Pneumoencephalogram, lateral view The thickness of the skull and the frontoparietal hyperostosis interna are more apparent here Observe the extreme atrophy of the frontal and parietal lobes, the dilatation of the lateral ventricles and the irregular outline of the roof of the lateral ventricles

brought out There was a mild facial weakness on the left, central in type The remaining cranial nerves were normal Muscular weakness was present in a mild form The biceps and triceps reflexes were very



Fig 4—Pneumoencephalogram, anteroposterior view, showing cortical atrophy, pronounced atrophy of the islands of Reil, moderate enlargement of the lateral ventricles and calcification of the falx just above the corpus callosum

prompt, and a radial periosteal reflex was present bilaterally A suggestive Hoffman sign was present in the left hand The abdominal reflexes were absent The knee jerks and ankle jerks were exaggerated, but

pathologic reflexes were not obtained. Coordination was unimpaired. The Romberg maneuver, station and gait were normal. Sensation was intact throughout in all modalities. The chest, abdomen and limbs showed no abnormalities. The temperature varied from normal to 99.4 F. The blood pressure was 118 systolic and 90 diastolic and the pulse rate 72. The third day after admission she had an "attack" described by the nurse as a "wave of tremors and spasms, rigid body, left eye turned outward, unable to talk and unable to move."

Roentgenograms of the skull showed an increased thickness and density of bone throughout the frontal, parietal and occipital regions. In addition, there were irregular hyperostoses of the inner table of the frontal and parietal bones. The sella turcica was small, and the clinoid processes were almost completely bridged. Calcification of the falx, measuring 4 mm by 2 cm, was present (figs 1 and 2).

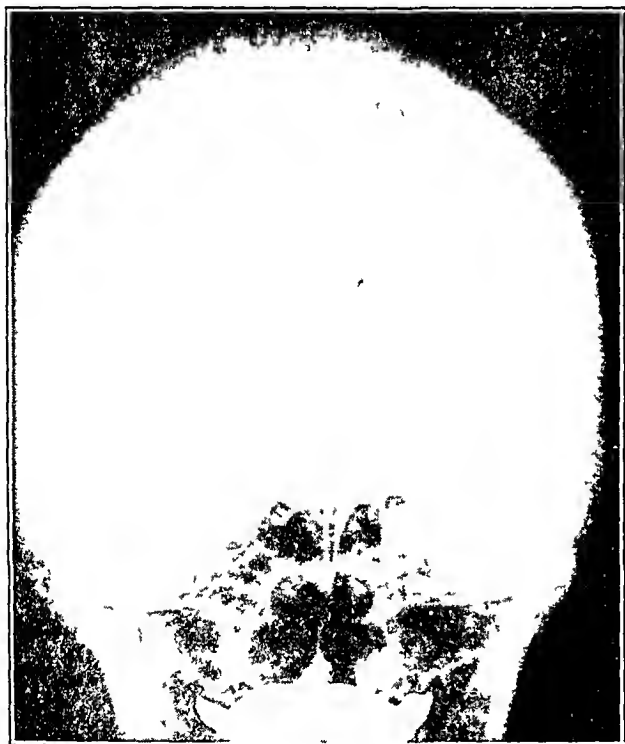


Fig 5—Pneumoencephalogram, posteroanterior view, showing enlarged, asymmetric lateral ventricles and the hyperostosis in relief.

In view of the roentgen findings of a thickened calvarium with frontoparietal hyperostosis interna associated with the neuropsychiatric phenomena, the diagnosis of Morgagni-Stewart-Morel syndrome was made. The similarity of many of the behavioral peculiarities, personality changes and mental symptoms to those of dementia paralytica prompted the performance of pneumoencephalography in the hope of finding some explanation in terms of intra-vitam cerebral changes.

Pneumoencephalography was performed on Nov 27, 1942. Spinal puncture, with the patient in the recumbent position, showed an initial pressure of 74 mm of cerebrospinal fluid. After 158 cc of cerebrospinal fluid had been removed and 150 cc of air injected in small amounts, there was still a free flow of fluid. The pneumoencephalograms showed pronounced cortical atrophy over the frontal and parietal lobes, atrophy of the islands of Reil and moderately advanced internal

hydrocephalus, with asymmetry and irregularity of the lateral ventricles (figs 3, 4 and 5). Laboratory studies showed normal blood cell count, normal results of urinalysis, normal cerebrospinal fluid, normal serologic reactions of blood and cerebrospinal fluid, blood calcium 11.2 mg per hundred cubic centimeters, blood phosphorus 2.5 mg and blood cholesterol 300 mg, basal metabolic rate, —23, —10 and +2, sugar tolerance, during fasting 70 mg at one-half hour 145 mg and at one hour 165 mg per hundred cubic centimeters, urinary creatinine, 549, 497 and 787 mg per liter on successive days, creatine + creatinine, 609, 1,224 and 860 mg per liter.

During the last ten days in the hospital she received some form of gelatin with each meal and an amino acid preparation. She believed there was slight improvement in her headache and an increase in strength. This report may have been unreliable, because after being discharged she refused treatment and expressed paranoid ideas.

#### COMMENT

Cases of the composite syndrome of hyperostosis frontalis interna with accompanying neuropsychiatric manifestations associated with cerebral atrophy pose a number of interesting questions. Are the mental symptoms related to the cerebral atrophy? Is the cerebral atrophy a secondary process caused by the impingement of the hyperostotic osteophytes? Is the cerebral atrophy primary and the hyperostosis a compensatory process? Are the bony and cerebral changes due to separate and unrelated mechanisms, or are they individual reactions of the tissues to essentially the same constitutional disturbances in the metabolic and endocrine spheres or perhaps to some as yet unidentified factor? Moore,<sup>1</sup> in describing the bony changes of what he termed "metabolic craniopathy," stated that "the skull does not increase in size—this fact is significant for the reason that the increased volume of the bone under these circumstances has to be accommodated at the expense of the capacity of the cranial cavity." This implies that the brain is involved either by direct pressure or by a disturbance secondary to diminished volume of blood or cerebrospinal fluid and indirectly implies that such changes could be responsible for the neuropsychiatric aspects of this syndrome. The similarity of the atrophy described in the case presented here to that seen in pneumoencephalograms in cases of dementia paralytica<sup>10</sup> would indicate that there is a relationship of the atrophic changes with the mental symptoms. Moreover, the pneumoencephalographic and autopsy evidence of cerebral atrophy in such conditions as presenile sclerosis (Alzheimer's disease), Pick's disease and pro-

10 Moore, M. T., Nathan, D., Elliott, A. R., and Laubach, C. Encephalographic Studies in Mental Disease, *Am J Psychiat* 92:43-67, 1935.

gressive subcortical encephalopathy (Schneider's disease), which present neuropsychiatric symptoms, again would substantiate the relationship between the atrophy and the nervous and mental symptoms. There is much disagreement regarding the question as to which comes first, that is, whether the cranial hyperostosis is followed by the cerebral degeneration or whether the process is the reverse. Morel<sup>4</sup> originally believed that the hyperostosis interna damaged the underlying brain directly, but later<sup>11</sup> he retracted this view and concurred with Grieg,<sup>81</sup> who expressed the opinion that the intracranial osteophytes did not of and by themselves produce cerebral damage or bring on mental symptoms. Others have maintained that the pressure exerted by the hyperostosis results in cortical degeneration, whereas Henschen,<sup>12</sup> Schneider<sup>13</sup> and Stewart<sup>14</sup> have presented convincing data that the pressure exerted by the frontal hyperostosis does not per se produce the neuropsychiatric signs and symptoms. The encephalograms (figs 3, 4 and 5) show that the areas of cortical atrophy are not in direct contact with the hyperostoses at all points but that fluid-filled spaces exist between the inner table of the skull and the brain. This observation would also preclude the contention that the hyperostosis fills in the "dead space" as a compensatory mechanism. Stewart<sup>14</sup> showed this conclusively in a report on a 68 year old woman presenting an advanced form of hyperostosis frontalis interna, stating

The brain showed a massive lobar softening of three years' duration, limited to the right cerebral hemisphere, the other hemisphere showing only a minor degree of senile atrophy. The opinion is expressed that this crossed relationship between the gross atrophy of the right cerebral hemisphere and the thicker left half of the pars frontalis lends no support for the view that in hyperostosis frontalis interna, reduction of the volume of the brain stimulates the deposit of new bone.

Roth<sup>15</sup> would make it appear that the cranial bony changes and the neuropsychiatric manifestations are of separate origin. He stated that "neurologic and mental sequelae, as a consequence of the presence of the hyperostoses, appear to

be quite infrequent"—this despite the fact that all of his 8 patients presented either psychiatric or neurologic conditions—and concluded that "the neuropsychiatric signs and symptoms were the result of other factors, such as cerebral arteriosclerosis, hypertension, etc." It must be borne in mind that the mental symptoms may antedate by as much as ten or twenty years<sup>5</sup> the final establishment of the diagnosis by the roentgenogram. The patient reported on here, aged 39, showed no evidence of arteriosclerosis, and blood pressure readings were low. Moreover, some of her symptoms were of ten years' duration. Knies and Le Fever<sup>5</sup> have reported frontal hyperostosis in a 7 year old boy, son of a 41 year old woman who had the symptom complex of hyperostosis frontalis interna, with endocrine and neuropsychiatric disturbances.

Hemphill and Stengel<sup>16</sup> reported the histopathologic observations in the case of a 65 year old patient presenting the syndrome of frontal hyperostosis. The brain exhibited a diffuse and focal loss of ganglion cells of the third and fifth, and to a lesser degree of the sixth, cortical layers in the frontal and parietal lobes. The cerebral blood vessels showed no marked changes. Pathologic changes were found in the anterior lobe of the pituitary, parathyroid, thyroid and adrenal glands. The encephalographic examination in the case herein reported revealed a degree of atrophy which histologically would be comparable to that described in the above case.

The patient reported on here had menstrual irregularities and imbalance of the vegetative nervous system. The laboratory data, showing the disparity of the abnormal calcium-phosphorus ratio, the high blood cholesterol level, low basal metabolic rate and disturbed sugar tolerance, are indicative of both metabolic and endocrine disturbances. Mortimer<sup>17</sup> and his associates have shown the relationship existing between calcium and fat metabolism and the function of the anterior lobe of the hypophysis and have expressed the belief that the Morgagni-Stewart-Morel syndrome results from endocrine dysfunction, mainly of pituitary origin. Others<sup>8</sup> also have offered an explanation for the varied symptoms on an endocrine basis. It appears, therefore, that this syndrome is in fact a constitutional disorder manifesting itself in a peculiar localized involvement of the cranial bones and a

11 Morel, F. L'hyperostose frontale interne, Schweiz med Wchnschr **67** 1235-1237, 1937

12 Henschen (footnote 8 c, f, g and h)

13 Schneider, E. Zur Kenntnis der Schadelosteome und der Hyperostosis frontalis, Med Klin **32** 487-490, 1936

14 Stewart, R. M. Hyperostosis Frontalis Interna Its Relationship to Cerebral Atrophy, J Ment Sc **87** 600-607, 1941

15 Roth, N. The Syndrome of Frontal Internal Hyperostosis, Am J Psychiat **98** 63-69, 1941

16 Hemphill, R. E., and Stengel, E. Morgagni's Syndrome. A Clinical and Pathological Study, J Ment Sc **86** 341-365, 1940

17 Mortimer, S. a. b. Mortimer, Levene and Rowe sc

biochemical and morphologic disturbance in the brain

In view of the fact that the Morgagni-Stewart-Morel syndrome often occurs in incomplete patterns, it would not be too hazardous at this time to venture the view that the cerebral changes occur, at a slow and irregular rate to be sure, *pari passu* with the metabolic craniopathy and reflect a reaction of the individual tissues to an altered metabolic state. When the craniopathy and endocrine manifestations predominate and no overt psychoneurosis or psychosis exists, then the Morgagni appellation is given; however, if in addition neuropsychiatric

disorders appear, the Stewart-Morel designation is attached

#### SUMMARY

A woman presented the syndrome of calvarial hyperostosis with metabolic, endocrine and neuropsychiatric disturbances (Morgagni-Stewart-Morel syndrome). Pneumoencephalographic studies showed evidence of cerebral degeneration in the form of frontoparietal cortical atrophy, atrophy of the islands of Reil, asymmetry of the lateral ventricles and moderate internal hydrocephalus.

1813 Delancey Street



# EFFECTIVENESS OF VARIOUS SULFONAMIDE DRUGS AND NEOARSPHENAMINE AGAINST PNEUMOCOCCI IN BONE MARROW CULTURES

## A COMPARATIVE STUDY

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In previous publications it has been shown that sulfanilamide is more effective against pneumococci in bone marrow cultures than antiserum is, that sulfanilamide plus antiserum is much more effective than either alone,<sup>1</sup> that sulfapyridine alone is much more effective than sulfanilamide plus antiserum and that sulfapyridine plus antiserum is definitely more effective than sulfapyridine alone.<sup>2</sup> Sulfathiazole has been shown to be much more effective against staphylococcal

infections than sulfapyridine.<sup>3</sup> The relative effectiveness of several sulfonamide drugs against pneumococci is presented in the present study.

The marrow culture method has proved to be effective for controlled, quantitative measurement of the action of therapeutic agents on bacteria in the presence of living human cells.<sup>4</sup>

## EXPERIMENTAL STUDY

About 50 cc of a culture which contained about 100,000,000 living human nucleated marrow cells in a medium which consisted of 35 per cent human cord serum obtained from the fetal side of the placenta and 65 per cent balanced salt solution<sup>5</sup> was placed in a 50 cc vaccine vial and inoculated with recently isolated virulent strains of various types of pneumococci from the

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Dr Bullowa wrote this paper from marrow culture data submitted to him by Dr Osgood. Because of a protracted illness, followed by death on Nov 9, 1943, he was unable to include the clinical data as planned.

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From the Medical Service of Harlem Hospital and the Department of Hospitals of the City of New York, Oswald LaRotunda, Director, from the Department of Medicine and the Division of Experimental Medicine, University of Oregon Medical School, and from the Littauer Pneumonia Research Fund of New York University College of Medicine.

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4 Osgood, E E. (a) Marrow Cultures, in *A Symposium on the Blood and Blood-Forming Organs*, Madison, Wis, University of Wisconsin Press, 1939, pp 219-241, (b) Culture of Human Marrow. Studies on the Mode of Action of Sulfanilamide, *J A M A* **110** 349-356 (Jan 29) 1938, (c) Culture of Human Marrow. Studies of the Relative Effectiveness of Neoarsphenamine, Mapharsen, Sulfanilamide, Sulfapyridine, Sulfathiazole, and Sulfamethylthiazole on Infections with Streptococcus Viridans (Alpha Hemolytic Streptococcus), *Am J M Sc* **200** 596-603 (Nov) 1940.

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pneumonia service of Harlem Hospital, New York After thorough mixing, pour plate colony counts were made, and equal volumes of culture were placed in each of six to eight 30 cc vaccine vials To each of these except one, which was left as a control, the desired concentration of one of the sulfonamide compounds to be tested was added The cultures were then placed in the incubator At intervals samples were removed from each vial, and pour plate colony counts and stained smears were made This technic insures that the cultures from one experiment are identical in every respect except for the drugs purposely introduced Examples of the types of results obtained in individual experiments are shown in tables 1 to 4 The stained smears from these experiments show the appear-

TABLE 1—*Experiment with Type VII Pneumococci*\*

	Hours			
	0	6	25	49
Control	180	24,600	270 000,000	
Sulfapyridine 1 20,000	180	750?		00
Sulfathiazole 1 20,000	180	250?		00
Sulfamethylthiazole 1 20,000	180	150?		1
Sulfaphenylthiazole 1 20,000	180	50,000	300,000,000	

\* The figures represent colony counts

ance which would be expected from the colony counts, as illustrated in figures 4 to 9 in an article by Schmith<sup>5a</sup>

Sulfapyridine and sulfathiazole were extremely effective against pneumococci In order to show a difference, comparatively large inoculations were used and a 1 20,000 concentration, which corresponds to 5 mg of the drugs per hundred cubic centimeters Even under these conditions, in the majority of the experiments both sulfa-

TABLE 2—*Experiment with Type V Pneumococci*\*

	Hours			
	0	27	30	54
Control	390	100 000,000		
Sulfapyridine 1 20,000	390		50	100 000
Sulfathiazole 1 20,000	390		4,000	30,000,000
Sulfamethylthiazole 1 20,000	390		30,000,000	250,000
Sodium sulfanilyl sulfanilate 1 20,000	390	100,000 000		

\* The figures represent colony counts

pyridine and sulfathiazole led to sterility after twenty-four to seventy-two hours, as is shown in table 1 They therefore appeared to be

5a Schmith, K Experimental Studies on the Effect of Sulfapyridine on Pneumococci and Gonococci, Copenhagen, Arnold Busck, 1941

equally effective (Against some strains, however, sulfapyridine was more effective than sulfathiazole [table 2], and against other strains sulfathiazole was more effective than sulfapyridine [table 3]) In the experiment summarized in table 1 sulfaphenylthiazole was completely ineffective, as was sodium sulfanilyl sulfanilate in the experiments reported in tables 2 and 3 Sulfamethylthiazole according to tables 2 and 3 was extremely effective, but it was definitely less effective as a rule than sulfapyridine and sulfathiazole, although there were occasional exceptions In table 4 sulfapyridine and sulfathiazole are shown to have been equally effective, sulfamethylthiazole of some value and sulfaphenylthiazole totally ineffective

Table 5 summarizes the results of the experiments As we have previously reported,<sup>6</sup> dif-

TABLE 3—*Experiment with Type VII Pneumococci*\*

	Hours		
	0	27	34
Control	280	100 000,000	
Sulfapyridine 1 20,000	280		9 800
Sulfathiazole 1 20,000	280		9 000
Sulfamethylthiazole 1 20,000	280	35	107
Sodium sulfanilyl sulfanilate 1 20,000	280		161,000

\* The figures represent colony counts

ferent strains of the same type of pneumococcus showed marked differences in susceptibility to these drugs The strain of type IV investigated in these experiments was relatively resistant to all of the drugs investigated, although in other experiments strains of type IV have been found which were highly susceptible to the action of sulfapyridine It is noteworthy that in 11 of the 22 experiments sulfapyridine and sulfathiazole led to sterility and thus were equally effective Sulfamethylthiazole led to sterility

TABLE 4—*Experiment with Type VIII Pneumococci*\*

	Hours			
	0	6	25	48
Control	820	17,800	100,000,000	
Sulfapyridine 1 20,000	820	400?	50	0
Sulfathiazole 1 20,000	820	100?	50	0
Sulfamethylthiazole 1 20,000	820	200?	50	70?
Sulfaphenylthiazole 1 20,000	820	300?	250 000 000	

\* The figures represent colony counts

in 7 of the 20 experiments in which it was used In 2 of the experiments with pneumococci of type VIII all three drugs were equally, but only slightly, effective This makes a total of 4 of the

6 Bullowa, Osgood, Bukantz and Brownlee<sup>2</sup> Osgood<sup>4</sup>

22 experiments in which sulfapyridine and sulfathiazole were equally effective and of 10 of the 20 in which sulfamethylthiazole was as effective as sulfapyridine and sulfathiazole. In 1 experiment sulfapyridine was definitely superior to sulfathiazole, and in 7 experiments sulfathiazole was superior to sulfapyridine. Neoarsphenamine was totally ineffective against all strains of pneumococci tested, hence data on tests with it are omitted from the tables.

From these observations it may be concluded that there is no reason ever to employ sulfamethylthiazole in the treatment of pneumonia, because both sulfapyridine and sulfathiazole offer more promise and are not as toxic. From the standpoint of absolute effectiveness under these conditions there is no choice between sulfapyridine and sulfathiazole.

TABLE 5—Comparative Effectiveness of Drugs Against *Pneumococci*\*

Type	Strain	Inoculation	Sulfa pyridine	Sulfa thiazole	Sulfa methyl thiazole
I	A	2	6	6	6
I	B	0	0	0	0
II		3	6	3	6
III		2	5	2	4
IV	A	3	8	8	8
IV	A	3	8	8	8
V	A	2	0	0	0
V	A	2	5	7	5
VII	A	1	0	0	8
VII	A	2	0	0	0
VII	A	3	5	2	3
VII	B	2	4	0	2
VII	B	2	3	1	5
VIII	A	2	0	0	0
VIII	A	2	0	0	0
VIII	B	3	8	5	6
VIII	B	3	7	5	7
XII	A	1	0	0	0
XII	A	3	0	0	0
XXV	A	2	0	0	
XXV	A	2	0	0	

\* The figures represent the logarithm of the final colony count.

This series of experiments employing a single concentration of the drugs was completed before sulfadiazine and sulfathiazoline (2-sulfanilyl-3,5-dihydrothiazole) were available. Later, observations were made employing several dilutions of each drug and several sizes of inoculum as well as different strains, because these are the factors which influence effectiveness. These results are shown in table 6. The observations of Schmith<sup>52</sup> that susceptibility of organisms may be described in terms of number of organisms and concentration of sulfapyridine to which they are vulnerable is supported by these results. A discussion of table 6 follows.

*Inoculation of 100 Organisms per Cubic Centimeter or Less*—With 20 organisms per cubic centimeter of a type IV strain (J H) of pneu-

mococci, sulfathiazole was superior to sulfadiazine. The culture was sterilized with 10 mg of sulfadiazine per hundred cubic centimeters but not with 5 mg, whereas sulfathiazole was effective with 5 mg per hundred cubic centimeters. With 24 organisms per cubic centimeter of a type VII strain (G S) of pneumococci, 5 mg of sulfathiazole per hundred cubic centimeters was effective, as was 20 mg of sulfadiazine per hundred cubic centimeters (the only concentration used). With 10 mg per hundred cubic centimeters sterilization by sulfathiazole occurred, though it was delayed. With an inoculum of 100 organisms per cubic centimeter of a type XII strain (R J) of pneumococci, 5 mg of sulfathiazole per hundred cubic centimeters, 20 mg of sulfadiazine and 10 mg of sulfathiazoline were effective. Sulfanilamide was ineffective.

*Inoculation of More than 100 Organisms per Cubic Centimeter and Less than 200*—Sulfathiazole was superior to sulfadiazine with an inoculum of 141 organisms per cubic centimeter of a type VII strain (G S) of pneumococci. Sulfadiazine sterilized in a concentration of 20 mg per hundred cubic centimeters but not in a concentration of 10 mg per hundred cubic centimeters, whereas 5 mg per hundred cubic centimeters of sulfathiazole produced sterility. With 128 organisms per cubic centimeter of a type IV strain (J H) of pneumococci, 5 mg per hundred cubic centimeters of sulfathiazole was as effective as 10 mg of sulfadiazine.

*Inoculation of 200 to 500 Organisms per Cubic Centimeter*—With 276 organisms per cubic centimeter of a type I strain (M Ben) of pneumococci, 20 mg of sulfadiazine per hundred cubic centimeters was slightly better than 5 mg of sulfathiazole per hundred cubic centimeters, but neither resulted in sterility. With 350 organisms per cubic centimeter of a type I strain (M Ben) of pneumococci, 5 mg of sulfathiazole per hundred cubic centimeters was better than 20 mg of sulfadiazine per hundred cubic centimeters in effecting sterility. With 330 organisms per cubic centimeter of a type I strain (M Ben) of pneumococci, 5 mg of sulfathiazole per hundred cubic centimeters was superior to 20 mg of sulfadiazine in effecting sterility. With 220 organisms of a type IV strain (B G) of pneumococci sterilization was not accomplished by 5 mg of sulfathiazole per hundred cubic centimeters or by 10 mg of sulfadiazine. With 458 organisms per cubic centimeter of a type VIII strain (L T) of pneumococci, neither sulfathiazole nor sulfadiazine in a concentration of 5 mg per hundred cubic centimeters resulted in sterility.

TABLE 6—Experiments in Which Different Concentrations of Drugs, Sizes of Inoculums and Strains Were Used

Case	Name of Patient	Pneumococcus Type	Drug	Concentration, Mg./100 Cc.	Initial Inoculum	Logarithm of Bacterial Population Hours After Inoculations						
						0	16-20	20-24	24-40	40-49	49-78	78-143
1	M B	I	Control	276	2.44	8.3						
			Sulfathiazole	5	2.44	5.98		6.75		8.3		
			Sulfadiazine	5	2.44	8.3						
			Sulfadiazine	20	2.44	4.90		5.59		6.72		
2	M B	I	Control	3.0	2.52	7.22			8.3			
			Sulfadiazine	5	2.52	4.63				6.90	8.3	
			Sulfadiazine	10	2.52	3.12				3.79	2.99	
			Sulfadiazine	20	2.52	7.02				2.78	2.57	
			Sulfathiazole	5	2.52	2.60				2.84		
3	C I	III	Control	670	3.83			7.91	7.34			
			Sulfadiazine	5	670	3.83		7.71	8.20	8.3		
			Sulfathiazole	10	670	3.83		4.05	4.20	4.65	5.74	
4	I H	IV	Control	20	1.3	8.3						
			Sulfadiazine	5	1.3	1.26				6.21		
			Sulfadiazine	10	1.3	2.0				0		
			Sulfadiazine	20	1.3	1.7				0		
4	I H	IV	Sulfathiazole	5	1.3	1.7				0		
			Control	980	2.99	8.3						
			Sulfadiazine	5	2.99	3.0				0		
			Sulfadiazine	10	2.99	2.0				0		
4	I H	IV	Sulfadiazine	20	2.99	1.7				0		
			Sulfathiazole	5	2.99	1.7				0		
			Control	128	2.11		8.3					
			Sulfathiazoline	5	2.11				0	0	0	
5	B G	IV	Sulfathiazoline	10	2.11				0	0	0	
			Sulfathiazoline	5	2.11				4.46	8.3		
			Sulfanilamide	10	2.11				4.40	7.1	7.85	
			Sulfadiazine	10	2.11				0	0	0	
			Sulfadiazine	20	2.11				0	0	0	
			Sulfathiazole	5	2.11				0	0	0	
			Control	220	2.34	8.3						
			Sulfathiazoline	5	2.34	5.65		7.38				
6	G S	VII	Sulfadiazine	5	2.34	7.87		9.3				
			Sulfadiazine	10	2.34	6.51		7.04				
			Control	24	1.38							
			Sulfathiazoline	10	1.38				1.40	0	0	
7	D M	VII	Sulfanilamide	10	1.38				4.96	8.3		
			Sulfadiazine	20	1.39				0	0	0	
			Sulfathiazole	5	1.39				0	0	0	
			Control	2 700	3.43		8.3					
7	D M	VII	Sulfadiazine	5	3.43		7.59	8.3				
			Sulfathiazole	5	3.43		4.25	4.70	8.3			
			Control	1 640	3.21				8.3			
8	D M	VII	Sulfadiazine	5	3.21			3.86			8.94	
			Sulfathiazole	5	3.21			7.04			0	
			Control	1 100	3.03	8.1						
8	L F	VIII	Sulfadiazine	5	1 100	3.07		4.48		4.76		8.3
			Sulfathiazole	5	1 100	3.03		3.71		2.3		4.33
			Control	458	2.66			7.79				
9	R J	XII	Sulfadiazine	5	458	2.66		7.04	7.55			
			Sulfathiazole	5	458	2.66		5.59	6.25	8.3		
			Control	100	2.0							
9	R J	XII	Sulfathiazoline	10	2.0				0	0	0	
			Sulfathiazole	5	2.0				0	0	0	
			Sulfanilamide	10	2.0				5.74	8.3		
			Sulfadiazine	20	2.0				0	0	0	

TABLE 7—Sources of Strains and Fates of Their Last Hosts

Pa- tient's Initials	Type of Pneu- coccus	Pa- tient's Age	Blood Cul- ture	Day of Disease Taken for Study	Involvement	Day of Disease			Total Grams Drug Given *	Total Days Drug Given	Highest Concen- tration	Day of Termi- nation	Results
						Day Serum Started	Total Dose of Serum, Units	Drug Started					
M Ber	I	50		8th	RUL	9th	196,000 rabbit					14th	Recovered
M Ben	I	35		2d	RUL RIL	4th	75,000 rabbit	4th	10 NaSp	2	7.6 on 5th	5th	Recovered
C T	III	32	Neg	5th	LLI	4th	140,000 rabbit	4th	19 Sp	4	4.7 on 6th	5th	Recovered
J H	IV	39	5-6 9-	6th	RML RIL	6th	617,500 rabbit	5th	25 Sd 7 NaSp	7 1	5.1 on 6th 6.1 on 8th 3.7 on 10th	10th (58 hr)	Recovered
B G	IV	46	Neg		Osteomyelitis of spine with sinus formation								Recovered
G S	VII	28	7	7th (spinal fluid)	LLL	7th		7th	18 Sp	6	3.7 on 8th 3.0 on 10th 3.5 on 12th	10th	Recovered
D M	VII	50	Neg	7th	Bronchitis						3.3 on		Recovered
L T	VIII	59	Neg	6th	RUL	6th		6th	18 Sd	3	3.3 on 7th	7th	Recovered
R J	XII	10 mo	Neg	Far and throat Jan 15 †	RIL RUI	8th	101,250 rabbit	2d	3.25 Sd 1.66 Sd	3 1	3.2 on 7th 6.7 on 8th 6.9 on 9th	7th	Recovered

\* NaSp indicates sodium sulfapyridine, Sp, sulfapyridine, and Sd sulfadiazine.

† The history is too incomplete to fix the day of the disease. The patient was admitted to the hospital on December 13.

*Inoculation of More than 500 Organisms per Cubic Centimeter*—With 670 organisms per cubic centimeter of a type III strain (C T) of pneumococci, 10 mg of sulfathiazole per hundred cubic centimeters was more efficient than 5 mg of sulfadiazine per hundred cubic centimeters, but sterility was not achieved. With 980 organisms per cubic centimeter of a type IV strain (J H) of pneumococci, sterility was achieved by sulfadiazine with 5, 10 and 20 mg per hundred cubic centimeters and with sulfathiazole with 5 mg per hundred cubic centimeters. When inoculums of 1,100 organisms per cubic centimeter of a type VII strain (D M) of pneumococci were employed, both sulfadiazine and sulfathiazole in a concentration of 5 mg per hundred cubic centimeters failed to sterilize, though bacteriostasis was more prolonged with sulfathiazole. This was also the case with 2,700 organisms per cubic centimeter of the same strain.

#### SOURCES OF STRAINS OF ORGANISMS STUDIED

The sources of the strains studied and the fates of their last hosts are shown in table 7. All of the patients recovered. The patients were treated on different days of illness, they were of different ages, and their illnesses, as measured by degree of involvement and of invasion of the blood were of varying severity. Different specific therapies were employed. On this account, the comparative effectiveness of the drugs cannot be inferred from the data on these cases. Since these observations were made, we have observed cases in which the organisms were unaffected by one of the drugs in concentrations usually accepted as satisfactory but in which a different drug, shown to be more efficacious by *in vitro* tests, has been successfully employed.

Some of the factors making for recovery from pneumococcal infection after treatment with sulfonamide drugs are in the individual case, such as duration of illness, duration of administration, responsiveness of tissues both humoral and cel-

lular, integrity of tissues, especially the kidneys and liver, and inhibitors in the blood or exudates, while other factors are more particularly related to the concentration of the sulfonamide compound maintained, its penetrability, toxicity and conversion and the damage done during excretion. In the clinical application of sulfonamide compounds it is necessary to consider the extent of the invasion, the previous experience of the invading strain and the immunity, active or passive, currently produced by the host. The concentration of organisms in the lungs as revealed by the examination of sputum may be as important as the degree of invasion of the blood. This is suggested by the observations on sputum of Frisch,<sup>7</sup> as well as by the inability to effect sterilization in heavily infected serous cavities or ulcerated areas, such as the cardiac valves.

#### CONCLUSIONS

The sulfonamide drugs differ in pneumococidal and pneumococcostatic activity. Usually sulfathiazole and sulfapyridine in a concentration of 5 mg per hundred cubic centimeters are equally active in destroying pneumococci. Sulfathiazole is more active against pneumococci than sulfadiazine in equal concentration, and than sulfathiazoline, sulfanilamide or sodium sulfanilyl sulfanilate. Neoarsphenamine is totally ineffective against pneumococci, while sulfadiazine, sulfathiazole and sulfapyridine are extremely effective. The concentration of organisms, as measured by the inoculum, and the concentration of the drug achieved and maintained are important factors influencing the therapeutic activity of the sulfonamide compounds. Very large inoculums were not sterilized by the concentrations usually employed clinically. Strains of pneumococci of the same type differed in their resistance to the same sulfonamide drugs in identical concentrations *in vitro*.

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# CAPILLARY FRAGILITY IN RELATION TO DIABETES MELLITUS, HYPERTENSION AND AGE

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In the course of investigating diabetic retinitis, many instances of increased capillary fragility were noted in the absence of blood dyscrasia or obvious vitamin C deficiency. For this reason it was considered important to investigate capillary fragility in diabetes, since the literature contains no record of such a study. Reported methods of determining this vascular abnormality vary so widely in technic and in interpretation that it was deemed necessary to evaluate the known methods before undertaking this investigation.

Capillary fragility is usually determined by one of two methods, either negative or positive pressure being used. The first method, introduced by Hecht,<sup>1</sup> consists essentially in application of negative pressure over a standard area of skin for a given period of time. Most of the subsequent investigators<sup>2</sup> have used a procedure in which a glass cup, 10 to 28 mm in diameter at the mouth, is pressed for one minute against the skin and the pressure within is reduced by a suction pump to a given degree of negative pressure, which is measured by an aneroid or mercury manometer. The pressure at which petechiae appear is considered the level of fragility. It is found that the capillary fragility varies considerably with the site of the cutaneous area tested. Hecht states that the fragility is less over the back and on the extensor surfaces of the arms. The end points considered as positive are also variable. Dalldorf<sup>3</sup> originally ad-

vised the determination of the pressure "necessary to produce several macroscopic petechiae easily seen with the unaided eye." O'Hara and Hauch,<sup>4</sup> however, said "Later it was decided [on the basis of a conference with Dalldorf] to adopt as the threshold reading the lowest negative pressure which, on casual inspection, gave an immediate impression that bleeding had occurred." Of their positive reactions about 80 per cent included 7 to 25 petechiae. As a rule, in readings which were considered negative there were from 0 to 10 petechiae.

Dalldorf,<sup>3</sup> in attempting to standardize the procedure, considered 30 mm as the average pressure for the outer position of the arm, and Elliott<sup>5</sup> reported a negative pressure of 20 to 35 mm of mercury as the normal range in the antecubital fossa. It has been stated that variations can occur before menses,<sup>2c</sup> with the climacterium,<sup>2c</sup> with psychic influences,<sup>2a</sup> with age,<sup>2c</sup> with the season<sup>6</sup> and with the hour of the day.<sup>1</sup> Moreover, even at a given time Roberts and her associates<sup>6</sup> have noted such variations in the two arms that they have averaged the readings of the two.

Most disturbing is the fact that O'Hara and Hauch<sup>4</sup> found that in the same subject the capillary resistance varies considerably at a given time in contiguous areas of skin and in the same area from day to day.

In view of these irregular findings, it was felt necessary to check this method. An apparatus was made consisting of a glass cup 1 cm in diameter, a hand pump and a mercury manometer. In performing the test precaution was taken not to pull the cup away from the skin until atmospheric pressure was restored in the interior of the cup. Tests were performed on

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hospitalized patients selected at random. The test on a given patient was performed at one sitting unless otherwise noted, and the number of petechiae at one or more pressure levels was noted.

Table 1 illustrates some of the results obtained with this method. It is evident that the test is not consistent or reliable, since contiguous areas of one arm at the same time show marked variations. For example, patients S C, B K and L G showed variations in the number of petechiae produced as a result of repeated tests at the same pressure. I R, R D and F G had fewer petechiae at greater negative pressures than at smaller negative pressures.

TABLE 1—*Capillary Fragility in Nondiabetic Non-hypertensive Patients Determined by Negative Pressure Method*

Name	Number of Petechiae at Negative Pressure of						
	10 Mm Hg	15 Mm Hg	20 Mm Hg	25 Mm Hg	30 Mm Hg	35 Mm Hg	40 Mm Hg
R P		1	3	1	3	3	
S C	1* 7 9	12 3	Innum- erable				
I R	1	10 6	13	4	11	3	14
R D		1	6 7	0 1	8		
F P			5 0	0 0	0 12 3	0 4	2 3
L R		3	0	10 3	3	0	1
F G	0	6 4	0	8	0	Innum- erable	
B K	8 4 1	3	0	2	20		
L G	15 4						

\* Multiple readings indicate tests on contiguous areas.

The positive pressure technic of Rumpel<sup>7</sup> (1909) and Leede<sup>8</sup> (1911) was therefore investigated. This consists in raising the venous and capillary pressure of the arm by means of a tourniquet or a Riva-Rocci cuff. The appearance of macroscopic capillary ruptures (petechiae) is the end point. All subsequent investigations were careful to define the conditions under which the test was carried out. The time of compression is either five minutes (Brock,<sup>2b</sup> Schrader<sup>2c</sup>) or

7 Rumpel. *Hautblutungen in Scharlach*, Munchen med Wchnschr 56 1404, 1909.

8 Leede, C. *Hautblutungen durch Stauung hervorgerufen als diagnostisches Hilfsmittel bei Scharlach*, Munchen med Wchnschr 58 293, 1911, *Zur Beurteilung des Rumpel-Leedeschen Scharlachphänomens*, ibid 58 1673, 1911.

fifteen minutes (Gothlin,<sup>9</sup> Wright<sup>10</sup>). The pressure used varies considerably 35 mm, 50 mm, to a point where "pulse is still palpable"<sup>2b</sup> or exactly between the systolic and the diastolic pressure.<sup>10</sup> The place of observation is the whole arm below the tourniquet or a circumscribed area, such as the antecubital fossa,<sup>9</sup> or a 2.5 cm circle 4 cm below the crease of the elbow on the flexor surface of the forearm.<sup>10</sup> The reading, usually done by good daylight or its equivalent, is either qualitative<sup>2c</sup> or quantitative.<sup>11</sup> It is of interest that none of the various authors stated whether single or repeated tests were used in drawing conclusions concerning the capillary fragility.

Bell and his co-workers<sup>12</sup> compared the results obtained on apparently healthy medical students with both positive (Gothlin) and negative (Dalldorf and Russell) pressure methods. They concluded that the results of each of the tests were consistent within themselves but that the results given by the two methods were not comparable. They suggested that possibly the two methods determine different functions of the capillaries. They were unable, however, to decide which of the two methods is to be preferred.

The method of Gothlin<sup>9</sup> was considered impractical by us, first, because the positive readings consist of small numbers of petechiae (2 to 6), which increases the chances of error through misinterpretation, second, because it requires using as many as three fifteen minute tests at three successively increased pressures for a given patient at one sitting. It is time consuming and may be frequently objected to by the patient.

Therefore, the following two methods were used in the present study.

(a) The qualitative-diastolic method. This consists of compressing the upper arm by a Riva-Rocci cuff for fifteen minutes at the patient's diastolic pressure. An estimate of the petechiae below the cuff was classified as "negative, slightly positive or definitely positive."

(b) The Wright modification of Gothlin's technic. This consists in application of a Riva-Rocci cuff to the upper arm for fifteen minutes (unless otherwise indicated) at a pressure half-

9 Gothlin, G F. *Outline of a Method for the Determination of the Strength of the Skin Capillaries and the Indirect Estimation of the Individual Vitamin C Standard*, J Lab & Clin Med 18 484, 1933.

10 Wright, I S, and Lilienfeld, A. *Pharmacologic and Therapeutic Properties of Crystalline Vitamin C*, Arch Int Med 57 241 (Feb) 1936.

11 Brock<sup>2b</sup> Gothlin<sup>9</sup> Wright and Lilienfeld<sup>10</sup>

12 Bell, G H, Lazarus, S, Munro, H N, and Scarborough, H. *Capillary Fragility (Resistance) Negative and Positive Pressure Test Compared* Lancet 2 536, 1942.

way between the patient's systolic and diastolic pressure. The petechiae were counted in a 2.5 cm circle on the flexor surface of the arm 4 cm below the crease of the elbow after waiting two to four minutes to allow the arm to regain its normal color. For a small number of patients fifteen minutes was intolerably long (especially at higher pressures) because of discomfort in the arm below the cuff. The readings were interpreted as follows: 0 to 20 petechiae as negative and over 20 as positive. In analyzing our results it was found useful to subdivide the positive readings into those with less and those with more than 50 petechiae. It may be of interest to mention that both the control and the diabetic patients usually showed small distinct petechiae, in

nor subsequent investigators have mentioned these factors, an independent control group was used.

RESULTS

In chart 1 are shown results based on a positive reaction with 20 petechiae or over and 1 with 50 petechiae or over. Capillary fragility was determined for 39 diabetic and 46 nondiabetic patients. All the patients were ambulatory and none had hypertension or other complications. The diabetes was of long duration and varied both in severity and in state of control. The percentage of patients who showed increased capillary fragility reached a peak in the fifth and sixth decades in both groups. There was a

TABLE 2—Capillary Fragility in Diabetic Patients

Name	Age	Systolic and Diastolic Blood Pressure, Mm Hg	Qualitative Diastolic Method				Wright Method			
			Number of Observations			Period of Observation	Number of Observations			Period of Observation
			Negative	Slightly Positive	Positive		0-10 Petechiae	20-50 Petechiae	50 Petechiae	
E. G.	50	190/70	0	2	1	5 months	0	0	4	2 months
F. G.	69	180/100	4	5	1	1. months	0	2	1	1 month
C. P.	67	150/80	3	4	3	10 months	0	1	4	2 months
A. K.	44	185/80	2	0	0	1½ years	0	2	1	1 month
R. P.	50	140/80	2	2	4	1 year	0	0	6	4 months
M. R.	54	135/75	8	5	4	15 months	1	0	4	4 months
A. S.	52	135/75	12	17	3	1 year	0	0	2	
R. B.	53	140/80	7	12	3	10 months	0	1	2	1 month
S. P.	61	185/90					1	5	3	2 months
S. W.	61	125/70					0	0	7	8 months
G. L.	63	150/70					0	0	4	3 months
S. B.	57	125/65					0	0	6	4 months
F. D.	55	145/80					0	0	7	8 months
F. G.	50	120/70	2	5	7	14 months				
F. G.	59	150/80	1	0	2	3 months				
B. N.	50	135/90	9	3	0	1 month				
B. S.	67	145/80	12	1		14 months				
F. S.	70	180/90	1	0	2	6 weeks				

contradistinction to the large confluent petechiae observed in persons with thrombopenic purpura and other blood dyscrasias.

Table 2 gives the results of positive pressure tests repeated over a period of one or more months on a group of diabetic patients. There was a variation in the results obtained in the same patient at different times, but this variation was greater in the case of the qualitative-diastolic method. The latter could be used, however, if sufficient numbers of tests were performed. Wright's method gave more uniform results. Accordingly, with this procedure a smaller number of tests are required.

In the study of the state of capillary fragility in diabetic patients it was deemed necessary to evaluate carefully the effect of age and of hypertension on the test. The presence of hypertension is especially important, since the height of the pressure at which the test is carried out varies with the blood pressure. Since neither Wright

greater incidence of increased capillary fragility in the diabetic as compared with the nondiabetic patients. It is interesting to note that similar

TABLE 3—Capillary Fragility in Diabetic Hypertensive Patients Determined Simultaneously at Test Pressure Levels of 100 Mm of Mercury and Midway Between Systolic and Diastolic Pressure

Name	Age	Systolic and Diastolic Blood Pressure, Mm Hg	Number of Petechiae	
			At Pressure Halfway Between Systolic and Diastolic	At Pressure of 100 Mm Hg
A. R.	60	160/90	135	46
H. S.	74	180/100	200	4
M. W.	58	160/95	63	120
L. S.	70	165/85	80	120
B. W.	71	165/85	140	0
A. O.	68	260/130	200	13
A. O.	58	180/100	200	100
N. T.	67	200/100	180	25
J. G.	70	210/90	56	45
S. F.	61	240/120	200	70
E. G.	69	180/105	400	170
I. O.	60	185/90	180	13
Percentage of patients with 50 petechiae or over			100	42



curves were obtained when 20 petechiae (Wright) and 50 petechiae were taken as the basis of a positive result

Chart 2 shows the results obtained in a study of the capillary fragility in 54 diabetic patients

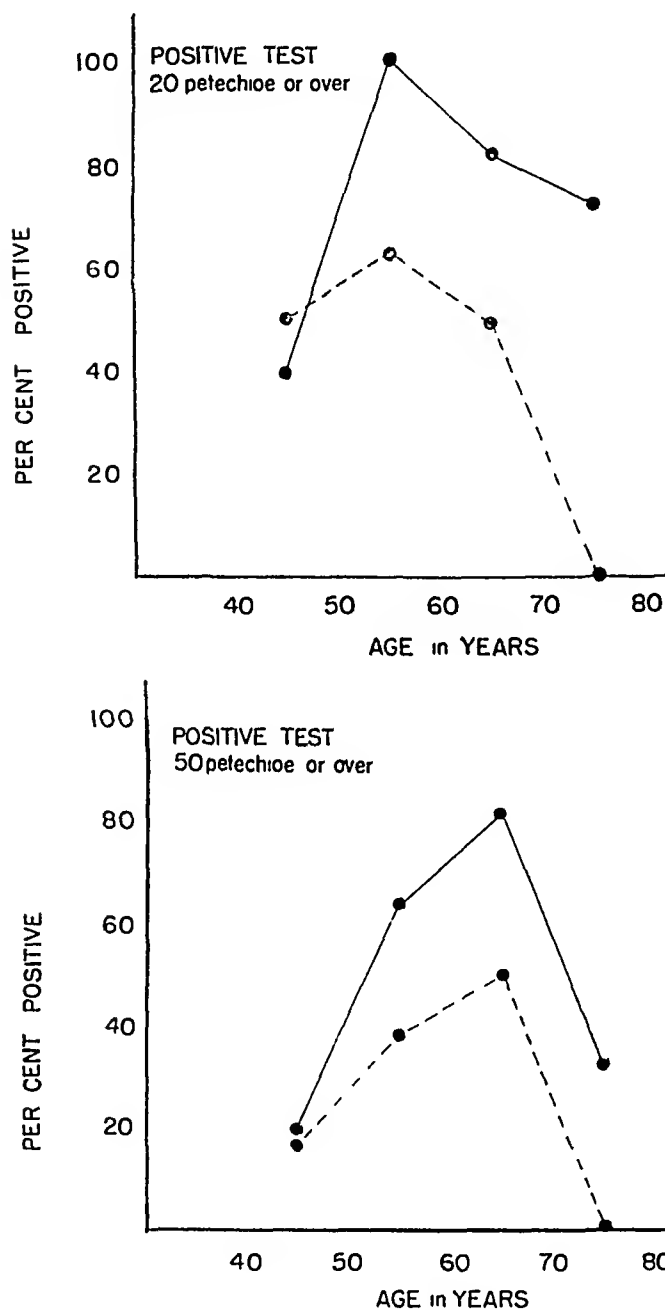


Chart 1—Frequency of increased capillary fragility in 39 diabetic (solid line) and 46 nondiabetic (broken line) patients in relation to age

(15 with hypertension) and 67 nondiabetic patients (21 with hypertension). Of the hypertensive patients with diabetes, 100 per cent showed increased capillary fragility, as compared with 53 per cent of the hypertensive patients without diabetes. Similarly the nonhypertensive patients with diabetes showed a higher incidence of increased capillary fragility (54 per cent) than those without diabetes (24 per cent). It is also evident that the subjects with hypertension showed a greater incidence of increased capillary fragility (53 per cent) than those without hypertension (24 per cent).

Since the pressure level at which the tourniquet test is carried out is higher in the case of hypertensive subjects (when the point midway between systolic and diastolic pressures is used), a comparison of the results at a lower pressure level (namely 100 mm, which is comparable to that used for nonhypertensive subjects) with those at higher levels was made. On 12 diabetic patients with hypertension such an experiment was performed as follows. On one arm the tourniquet test was performed at a pressure of 100 mm and on the other at the usual higher level.

As shown in table 3, all patients exhibited increased capillary fragility at the higher pressure and only 42 per cent at the lower pressure (50 petechiae being used as the end point). Referring to chart 2, it is noted that of the diabetic patients without hypertension, whose test pressure was about 100 mm of mercury, 54 per cent had a positive reaction to the tourniquet test, while of the diabetic patients with hypertension only 42 per cent had a positive reaction to that test (table 3) at the same pressure level of 100. This suggests that in the case of hypertensive patients the level of pressure at which the test is performed rather than the tension per se is respon-

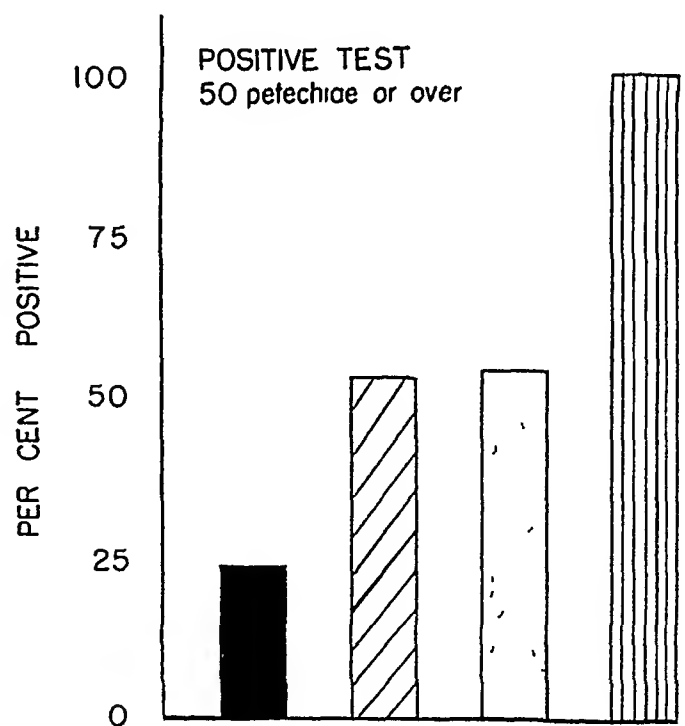


Chart 2—Frequency of increased capillary fragility in 39 nondiabetic nonhypertensive patients (solid bar), 45 nondiabetic hypertensive patients (diagonal lines), 21 diabetic nonhypertensive patients (dots) and 15 diabetic hypertensive patients (vertical lines)

sible for the high percentage of positive reactions to capillary fragility tests. Further study is necessary to determine the proper pressure at



which the tourniquet test should be performed on hypertensive persons for the determination of capillary fragility

The results shown in chart 2 indicate that, irrespective of the validity of the fragility test in the presence of hypertension, there is a definitely increased capillary fragility in diabetic patients as compared with nondiabetic persons of the same age. Further, from chart 1 it is evident that the incidence of increased capillary fragility in persons with diabetes parallels that of nondiabetic subjects with increasing age.

#### CONCLUSIONS

Various methods for measuring capillary fragility have been investigated. Negative pressure methods were found to be unreliable. Of the positive pressure methods tried on a group of diabetic patients, Wright's method gave the most reliable results.

A group of 54 adult patients (15 with hypertension) and 67 nondiabetic patients (21 with hypertension) were tested by Wright's method. The incidence of increased capillary fragility was greatest in the fifth and sixth decades. The diabetic patients showed a greater incidence of increased capillary fragility at each age decade than the nondiabetic subjects.

In diabetic hypertensive patients the test showed a greater incidence of increased capillary fragility at the higher pressure levels (midway between systolic and diastolic pressure), as used by Wright, than at a lower arbitrary level (100 mm of mercury) when performed simultaneously on the two arms.

Without further study no conclusions can be drawn concerning the proper pressure at which the positive pressure test should be performed on hypertensive patients.

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# VITAMIN THERAPY IN INCREASED CAPILLARY FRAGILITY OF DIABETES MELLITUS

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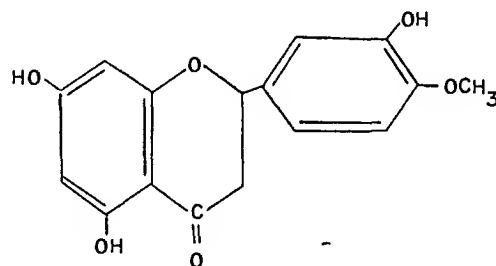
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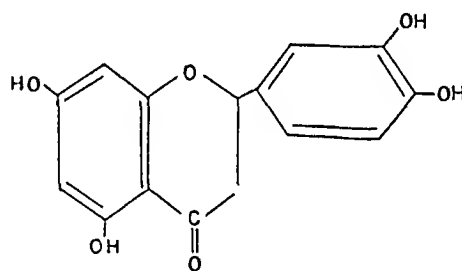
BOSTON

In 1936 Szent-Gyorgyi and his associates<sup>1</sup> isolated a crystalline substance from lemons which they called citrin. They<sup>1a</sup> found that this substance corrected the increased capillary fragility in guinea pigs on a scorbutogenic diet and in human beings with certain pathologic conditions. They called it vitamin P. Subsequently, studies both on animals and on human beings were carried out by numerous investigators. It was shown that citrin, a flavanone glucoside, is composed of two fractions, hesperidin glucoside<sup>2</sup> (formula I shows the aglycone), which is insoluble in water and is stable, and eriodictyol glucoside (formula II shows the aglycone), which is water soluble and sensitive to oxidation. Eriodictyol is demethylated hesperidin and contains the unstable orthohydroquinone group. It has been reported<sup>1b</sup> that the relative amounts of these substances in citrin vary with the ripening of the fruit used in its preparation and with the method of isolation. However, in most of the publications concerning therapy no indication of the relative amounts of the two fractions in citrin prepared according to Szent-Gyorgyi's method is given. It has also been shown that hesperidin is readily converted by alkali to the open ring chalcone (3,2',4',6'-tetrahydroxy-4-

methoxychalcone glucoside)<sup>3</sup>. Wawra and Webb<sup>3a</sup> postulated that hesperidin in this form is attached to protein through the  $\alpha$ ,  $\beta$  unsaturated ketonic group. They suggested that the chalcone is the biologically active component of citrin. They have further shown that after conversion of hesperidin to the chalcone by treatment with



HESPERIDIN AGLYCONE I



ERIODICTYOL AGLYCONE II

From the Medical and Surgical Services of the Beth Israel Hospital

Aided by a grant from the Charlton Research Fund, Tufts College Medical School

1 (a) Rusznyak, S, and Szent-Gyorgyi, A. Vitamin P. Flavonols as Vitamins, Nature, London **138** 27, 1936. (b) Armentano, L, Bentsath, A, Beres, T, Rusznyak, S, and Szent-Gyorgyi, A. Ueber der Einfluss von Substanzen der Flavongruppe auf die Permeabilität der Kapillaren. Vitamin P, Deutsche med Wchnschr **62** 1325, 1936. (c) Szent-Gyorgyi, A. Methoden zur Herstellung von Citrin, Ztschr f physiol Chem **255** 126, 1938.

2 (a) Bruckner, V, and Szent-Gyorgyi, A. Chemical Nature of Citrin, Nature, London **138** 1057, 1936. (b) Wilson, C W. A Study of the Boric Acid Color Reaction of Flavone Derivatives, J Am Chem Soc **61** 2303, 1939.

alkali in the cold the chalcone may be precipitated by acidification and that in crystalline form it slowly reverts to hesperidin. If the chalcone is indeed the biologically active constituent of citrin, the results of therapeutic tests with hesperidin depend to a large extent on the manner in which it is handled, such as treatment with alkali at some stage in its isolation, the length of time it stands in crystalline form or in solution before use, and whether the oral or the intravenous route of administration is employed. These factors may be considered, in part, as a

3 (a) Wawra, C Z, and Webb, J L. The Isolation of a New Oxidation-Reduction Enzyme from Lemon Peel (Vitamin P), Science **96** 302, 1942. (b) Wilson<sup>2b</sup>

reason for the conflicting reports on the efficacy of vitamin P therapy

In addition, in observations on man, the effectiveness of the therapy has been judged to a large extent by the result of some type of capillary fragility test. In the reports in which the method of measurement is given, the negative pressure method, which we consider unreliable, was commonly used (table 1)

In a previous communication<sup>4</sup> we have discussed the pitfalls of interpretation of data obtained by the various methods for determining capillary fragility, which explain in part the discrepancies in the literature as to the therapeutic results. The negative pressure method was found to be unreliable because of the variability of the findings in the same patient at a given time. The Wright positive pressure method can be utilized only if age and blood pressure are taken<sup>4</sup> into consideration in accordance with findings previously pointed out.

A review of the literature (table 1) indicates that citrin was tried in a wide variety of cases with increased capillary fragility irrespective of the underlying disease. For example, it was used in treatment of such widely differing syndromes as tuberculosis, pleurisy, myxedema and multiple myeloma. Conclusions of doubtful validity were drawn from some cases in which clinical bleeding alone was used as a criterion of therapeutic effectiveness, many of them cases of self-limited diseases, such as measles, arsenic intoxication and nephritis.

This is a report of the effects of various substances containing vitamin P and of purified components of citrin, hesperidin and eriodictyol in diabetic patients with increased capillary fragility as measured by positive pressure methods. Most of the preparations were given orally, but to a few long and well studied diabetic patients the purified hesperidin and eriodictyol were administered intravenously. In addition, the increased capillary fragility in 2 cases of thrombopenic purpura and in 1 case of rheumatoid arthritis was treated by intravenous injection of hesperidin and eriodictyol.

#### METHODS

To determine capillary fragility the Wright<sup>5</sup> quantitative positive pressure method was used. These observations were subject to the reservations for patients' age and blood pressure which were pointed out in a previous communication<sup>4</sup>. For a preliminary series of

patients the qualitative positive pressure test, in which the diastolic pressure was maintained for fifteen minutes and an estimate made of the number of petechiae on the forearm and dorsum of the hand, was used in determining a negative, slightly positive or markedly positive result.

Patients exhibiting an increased capillary fragility were used as test subjects. Before therapeutic tests were undertaken, the presence of increased capillary fragility was confirmed by repeated tests performed over a period of at least several weeks and in some cases many months. All of the patients had diabetes, except for 2 with thrombopenic purpura and 1 with rheumatoid arthritis.

A course of vitamin C therapy was instituted before vitamin P therapy was undertaken except for 2 patients both of whom had a normal level of vitamin C in the plasma<sup>6</sup>. The dissociation between the therapeutic effects of vitamins C and P has been emphasized by Scarborough and his associates<sup>7</sup> and also observed by Shwachman and Gould<sup>8</sup>. The latter found that vitamin C administered to scorbutic guinea pigs stimulated the phosphatase-producing centers, but they failed to obtain this with our preparations of eriodictyol and hesperidin,<sup>9</sup> which they gave intraperitoneally, singly and in combination.

In one series an exhaustive course of oral administration of vitamins C and B complex<sup>10</sup> was given before treatment with vitamin P was started. Vitamin P was administered in several forms,<sup>10</sup> as follows:

1 Fresh lemon juice

2 Fresh crude lemon-hot water extract, given orally according to the method recommended by the research laboratory of the California Fruit Growers' Exchange<sup>11</sup>

3 Tablets containing 0.25 Gm of hesperidin, given orally (found by the hot alkali test<sup>12</sup> to contain only traces of eriodictyol)

4 Hesperidin which was prepared in crystalline form from the finely powdered tablets by a continuous extraction with hot diethylene dioxide (dioxane) and crystallization from diethylene dioxide and acetone as fine pale yellow crystals. These gave a negative reaction for eriodictyol with hot potassium hydroxide solution. This

6 Blood vitamin C was determined as plasma ascorbic acid by the method of R. L. Mindlin and A. M. Butler (The Determination of Ascorbic Acid in Plasma: A Macromethod and Micromethod, *J Biol Chem* **122**: 673, 1938). The normal range of plasma ascorbic acid during fasting was considered 0.8 to 1.4 mg per hundred cubic centimeters of blood.

7 Scarborough, H., and Stewart, C. P. Effect of Hesperidin (Vitamin P) on Capillary Fragility, *Lancet* **2**: 610, 1938.

8 Shwachman, H., and Gould, B. S. Serum Phosphatase in Experimental Scurvy, *J Nutrition* **23**: 271, 1942.

9 Shwachman, H., and Gould, B. S. Personal communication to the authors.

10 Vitamin C tablets and vitamin B complex capsules were supplied by the Hoffmann-La Roche, Inc., of Nutley, N. J.; hesperidin tablets, by Glaxo Laboratories Ltd., of Greenford, England, through Ayerst, McKenna and Harrison Ltd., of Montreal, Canada, and calcium eriodictate, by Abbott Laboratories, North Chicago, Ill.

11 Lorenz, A. J., and Arnold, L. J. Personal communication to the authors.

12 Huszak, S. Ueber das Schicksal parenteral eingelegter Citrinlösung in Tierkörper, *Ztschr f physiol Chem* **249**: 214, 1937.

4 Beaser, S. B., Rudy, A., and Seligman, A. M. Capillary Fragility in Relation to Diabetes Mellitus, Hypertension and Age, *Arch Int Med*, this issue, p 18.

5 Wright, I. S., and Lilienfeld, A. Pharmacologic and Therapeutic Properties of Vitamin C, *Arch Int Med* **57**: 241 (Feb.) 1936.

TABLE 1—*Summary of Reports on the Use of Vitamin P Clinically*

Disease	Preparation Method of Adminis- tration and Dosage	Test Method	Therapeutic Effectiveness	Number of Cases	Author	Comments Concerning Capil- lary Fragility
1 Vascular purpura	Citrin solution intra- venously, 20-40 mg per day for 8-12 days	Negative pressure	Good	3	Armentano, Bentsath, Beres Rusznayak and Szent Gyorgyi <sup>1b</sup>	Negative pressure method unreliable
2 Vascular purpura	Citrin solution intra- venously	Clinical bleeding	Good	2	Lajos, S. Klein Wehnsehr 16 1615, 1937	Unreliable test method
3 Vascular purpura	Citrin solution intra- venously, 50 mg per day for 6 weeks	Negative pressure	Good after 6-10 weeks		Jersild, T. Lancet 1 1445, 1938	Negative pressure method unreliable and question of spontaneous remission
4 Thrombopenic purpura	Citrin solution intra- venously, 20-40 mg per day for 8-12 days	Negative pressure	Equivocal	4	Armentano, Bentsath, Beres, Rusznayak and Szent Gyorgyi <sup>1b</sup>	Negative pressure method unreliable
5 Thrombopenic purpura		Clinical course	None		Rosenthal, N. J. A. M. A 112:101, 1939	
6 Thrombopenic purpura	Citrin solution intra- venously, 50 mg twice in 4 weeks	"Tourni- quet test" of capillary fragility and plate- lets	None		Vaughan, M. Brit. M. J. 2 842, 1937	
7 Thrombopenic purpura	Citrin solution and vitamin C, intra- venously	Bleeding time and platelet counts	Good	5	Decker, C. T. Munchen med Wehnsehr 86 292, 1939	Unreliable method
8 Thrombopenic purpura	Citrin solution intra- venously, 25-60 mg per day and orally 25 mg per day	Negative pressure	Good	2	Vacek, V. Schweiz. med Wehnsehr 71 155, 1941	Negative pressure method unreliable
9 Leukemia	Citrin orally, 50 mg per day	Develop- ment of petechiae	Good	2	Vacek. Ibid	Unreliable test method, no fol- low up
10 Multiple myel- oma	Citrin solution intra- venously, 40 mg	Clinical bleeding	Stopped for 2 days		Vacek. Ibid	Unreliable test method
11 Vitamin defi- ciency purpura	Hesperidin tablets orally, 1 Gm	Negative pressure	Good	6	Searborough	Negative pressure method unreliable
12 Vitamin defi- ciency purpura	Citrin solution intra- venously, 50 mg per day	Clinical bleeding	Good		Jersild, T. Lancet 1 632 1939	Unreliable test method
13 Infectious dis- eases, measles	Hesperidin tablets orally, 0.25 Gm every 2 hours	Clinical bleeding	Good in 24 hours		Miller, A. A. Brit. J. Child Dis 38 1, 1941	
14 Endocarditis	Citrin solution intra- venously, 20-40 mg for 8-12 days	Negative pressure	Equivocal		Armentano, Bentsath, Beres Rusznayak and Szent Gyorgyi <sup>1b</sup>	Unreliable test method
15 Staphylococci sepsis, periton- itis, tuberculo- sis, pleurisy	Citrin solution intra- venously, 20-40 mg for 8-12 days	Negative pressure	Equivocal	3	Armentano, Bentsath, Beres Rusznayak and Szent Gyorgyi <sup>1b</sup>	Unreliable test method
16 Arthritis	Citrin solution intra- venously, 20-40 mg for 8-12 days	Negative pressure	Equivocal		Armentano, Bentsath, Beres Rusznayak and Szent Gyorgyi <sup>1b</sup>	Unreliable test method
17 Nephritis	Citrin solution intra- venously, 20-40 mg for 8-12 days	Negative pressure	Equivocal		Armentano, Bentsath, Beres, Rusznayak and Szent Gyorgyi <sup>1b</sup>	Unreliable test method
18 Hemorrhagic nephritis	Citrin solution intra- venously, 25-50 mg	Urinary bleeding	Shortened course		Lajos, S. Klein Wehnsehr 16 1615, 1937	Unreliable test method
19 Hemorrhagic nephritis	Citrin solution intra- venously, 30 mg for 2-4 days	Count of urine red blood cells	None	7	Gimsing, T. Ugeskr. f. Leger 101:117, 1939	Unreliable test method
20 Ulcerative colitis	Citrin solution intra- venously and citrin orally, 20-150 mg	Rectal bleeding	Good		Vacek, V. Schweiz. med Wehnsehr 71 155, 1941	Unreliable test method
21 Arsenic poison- ing	Hesperidin tablets orally, 0.25-1.0 Gm for 4-8 days	Negative pressure	Good	2	Horne, G., and Searborough H. Lancet 2 66 1940	Unreliable test method
22 Arsenic poison- ing	Hesperidin tablets orally, 0.25-1.0 Gm every 2 hours	Urinary bleeding	Good		Gornie, D. R. Lancet 1 1005 1940	Unreliable test method
23 Myxedema	Citrin solution intra- venously, 20-40 mg per day for 8-12 days	Negative pressure	Equivocal		Armentano, Bentsath, Beres, Rusznayak and Szent Gyorgyi <sup>1b</sup>	Unreliable test method
24 Increased capil- lary fragility in children	Calcium eriodictate orally, 25 mg per day for 1 week or more	Positive pressure (Wright), 40-75 pete- chiae	Equivocal	6	Rapaport, H. G. and Klein S. J. Pediat 18 321, 1941	Variations during control periods were considerable and not very posi- tive at onset
25 Diabetes	Citrin solution intra- venously, 20-40 mg per day for 8-12 days	Negative pressure	None	2	Armentano, Bentsath, Beres, Rusznayak and Szent Gyorgyi <sup>1b</sup>	Unreliable test method

material was given intravenously as a freshly prepared solution of 300 mg in 0.2 normal sodium hydroxide solution (2 cc) sterilized by heating at the boiling point for one minute just before administration

5 Eriodictyol as the calcium salt, which was dissolved in water just before intravenous administration. This orange-brown powder gave a strongly positive red color with hot potassium hydroxide solution, confirmatory of the presence of eriodictyol.

### RESULTS

The first group studied consisted of 4 diabetic patients who had in common a definitely increased

The second group consisted of 6 diabetic patients with retinitis and increased capillary fragility treated for many months with large oral doses of vitamin C and vitamin B complex and lemon juice as a source of vitamin P. The capillary fragility, followed by the qualitative method, showed no improvement as a result of this therapy (table 3). In the 4 cases in which determinations of blood vitamin C were made prior to the institution of the therapy, the values were normal. Saturation of the patients with vitamin C was confirmed by repeated determina-

TABLE 2—Effect of Vitamin C and P Therapy\* on Increased

	Age	Blood Pressure, Mm Hg	Pressure at Which Test Was Performed, Mm Hg	Capillary Fragility Test (Wright), No. of Petechiae		Vitamin C Therapy for 2 Weeks, Mg Ascorbic Acid per Day	Blood Vitamin C Levels	
				Before Treatment	One Month Later		Before Therapy	After Therapy
1	55	140/80	95	100	200	200	0.36	1.5
2	57	125/85	95	105	150	200	0.42	1.4
3	61	125/70	100	150	125	0	1.2	
4	63	150/70	115	200	200	0	1.1	

\* From left to right, this table is a chronologic record of successive therapeutic trials.

TABLE 3—Effect of Vitamin Therapy (C, B, P) on Increased Capillary Fragility in Diabetic Patients

Oral Treatment †												Capillary Fragility Test (Qualitative Method) After Vitamin Treatment
		Blood Pressure, Mm Hg	Fasting Initial Blood Vitamin C, Mg per 100 Cc *	Capillary Fragility Test (Qualitative Method) Before Treatment	Vitamin C		B Complex ‡		Lemon Juice			
Name	Age				Mg Daily	Dura tion of Therapy, Weeks	Cap sules Daily	Dura tion of Therapy, Weeks	Lemons Daily	Dura tion of Therapy, Weeks		
5	B L	44	120/ 80		Positive	300	0	3	24	1	8	Positive
6	F G	50	130/ 80	0.9	Positive	150	15					Positive
						150	4	3	3	2	6	
						200	2	6	29			
						400	6					
7	C P	67	160/ 80	0.9	Positive	300	5	3	6	1	5	Positive
8	E G	69	180/100	1.0	Positive	100	1	6	7	12	6	Positive
9	R P	50	140/ 80	0.9	Positive	150	2	3	2			Positive
						300	6					
						300	1	6	12	2	3	
						500	5			4	3	
10	M R	54	130/ 80		Positive	200	1	3	14	2 3	9	Positive
						400	2			2	10	
						100	1					
						300	6					

\* Blood vitamin C was determined by the method of Mindlin and Butler.<sup>6</sup>

† Vitamin C excretion in the urine on repeated examination was high in all cases.

‡ Berocca B complex perles, containing the total components of natural vitamin B complex (including nicotinic acid and vitamin B<sub>6</sub> [pyridoxine]) in potencies as found in dried brewers' yeast, 200 mg per perle, and fortified with thiamine hydrochloride to total 300 U. S. P. units of vitamin B<sub>1</sub> and with riboflavin to total 100 micrograms per perle.

capillary fragility and no other discernible disease, even hypertension. After a control period of determinations of capillary fragility they were treated successively with vitamin C given orally (see table 2), vitamin P given orally (hesperidin tablets) and a combination of the two. No significant change in the capillary fragility was noted on repeated tests as a result of this oral therapy. It is noteworthy that in 2 patients who had a low level of vitamin C in the blood a rise of this level to normal was not accompanied by improved capillary fragility.

tions of urinary vitamin C during the course of treatment. In spite of high levels of excretion, which indicated saturation, capillary fragility remained unimproved. No demonstrable effect on the retinitis was noted.<sup>13</sup>

The third group consisted of 6 patients: 3 with diabetes, 1 with rheumatoid arthritis, 1 with primary thrombopenic purpura and 1 with thrombopenic purpura secondary to aplastic

13 All these patients have been repeatedly examined ophthalmologically by Dr. E. E. Covitz, of the ophthalmologic clinic.

anemia (following use of anacin, a proprietary preparation containing acetophenetidin and acetylsalicylic acid with quinine sulfate and caffeine) Two of the diabetic patients (patients 9 and 10, tables 3 and 4) had previously received extensive oral therapy without benefit

These patients all had abnormal capillary fragility They were all given hesperidin intravenously, 3 received a course of intravenous injections of calcium eriodictate following the treatment with hesperidin, and 1 patient subsequently received, in addition, a combination of

be an exaggeration of a normal tendency in relation to age, and thus it may be another indication that diabetic patients are aging earlier This does not reveal its pathogenesis Since a deficiency in vitamins C and P was considered a possible cause of the increased capillary fragility in diabetic patients, it was necessary to check the diets of our patients for their content in vitamins C and P No deficiency in the intake of these vitamins was found The therapeutic results with vitamin C indicate that the increased capillary fragility in our patients could not be

#### Capillary Fragility in Nonhypertensive, Diabetic † Patients

Capillary Fragility Test After Vitamin C Therapy, No of Petechiae	No of Weeks of Oral Vitamin P Therapy (Hesperidin 1 Gm Daily)	Capillary Fragility Test After Vitamin P Therapy, No of Petechiae	Combined Vitamin C and Vitamin P (Hesperidin) Therapy for 2 Weeks		Capillary Fragility Test After Cessation of Therapy, Number of Petechiae		
			Vitamin C Daily	Hesperidin Daily, Gm	Immediately	Three Weeks	Four Months
150	3	72	200 mg ascorbic acid	1	150	150	170
150	3	100	200 mg ascorbic acid	1	85	70	
	3	120	6 oranges, 1 lemon	1	100	100	150
	3	200	9 oranges	1	200		

† Diabetes was moderately well regulated, and no patient had retinitis

TABLE 4—Therapeutic Administration\* of Vitamin P Intravenously

	Name	Age	Diagnosis	Capillary Fragility † Before Therapy, Number of Petechiae	Hesperidin Therapy Intravenously, Mg per Day	Capillary Fragility † After Hesperidin Therapy, Number of Petechiae	Calcium Eriodictate Therapy Intravenously, Mg per Day	Capillary Fragility † After Calcium Eriodictate Therapy, Number of Petechiae	Calcium Eriodictate and Hesperidin Intravenously, Mg per Day	Capillary Fragility † After Calcium Eriodictate and Hesperidin Therapy, Number of Petechiae
9	M R	56	Diabetic retinitis	100	200 for 10 days	120	100 for 10 days	120		
10	R P	51	Diabetic retinitis	200	200 for 9 days	200	100 for 10 days	200	100 of each for 10 days	160
11	M R	61	Diabetes, peripheral vascular disease	100	200 for 7 days	115				
12	A H	52	Rheumatoid arthritis	150	200 for 10 days	80				
13	J F	56	Primary thrombopenic purpura	200	200 for 9 days	200	100 for 12 days	200		
14	M P	32	Thrombopenic purpura aplastic anemia	90	200 for 7 days	110				

\* From left to right, this table is a chronologic record of successive therapeutic trials

† Capillary fragility was determined by the Wright positive pressure method

the two intravenously No beneficial effect was noted

#### COMMENT

Our previous study<sup>4</sup> showed that capillary fragility varied with both age and the patient's blood pressure (which determines the pressure level at which the test is performed) but that the diabetic patients had a higher incidence of increased capillary fragility in each age group We also noted that both the control and the diabetic patients usually showed small, distinct petechiae, in distinction to the large, confluent petechiae observed in persons with thrombopenic purpura and other blood dyscrasias

So far no explanation has been found for the increased capillary fragility in diabetes It may

attributed to latent scurvy This has been further proved by the normal level of vitamin C in the blood as well as the vitamin C saturation of the tissues as reflected in high urinary excretion of ascorbic acid Impairment in the absorption of vitamin P was ruled out by the use of intravenous administration Our negative results with vitamin P given orally confirmed the observations of previous investigators on its lack of effectiveness (table 1) It was therefore necessary to try in addition the administration of the two principal constituents of citrin, hesperidin and eriodictol, intravenously, separately and combined The negative results obtained in this experiment on a group of our patients add further proof of the ineffectiveness of vitamin P

on increased capillary fragility in the diseases mentioned. Hesperidin was given intravenously as a freshly prepared alkaline solution. It is probable that the greater part of the hesperidin existed under these conditions as the open ring chalcone, thought by Wawra and Webb<sup>3a</sup> to be the biologically active component of citrin.

#### SUMMARY

A review of the literature on the clinical use of vitamin P reveals that various forms of vitamin P have been used, but with no clear notion as to what component of citrin was being tested. Such therapy was studied in a wide variety of cases with increased capillary fragility irrespective of the underlying disease, which was frequently a self-limited disease. Conclusions of doubtful validity were drawn in some cases when the criterion of therapeutic effective-

ness was clinical bleeding or the result of a negative pressure test for determining capillary fragility.

The effectiveness of oral administration of vitamin C and the B complex on the increased capillary fragility in diabetic patients with and without retinitis has been tested, with negative results.

The effectiveness of both orally and parenterally administered vitamin P in some patients of this group was studied. Both the hesperidin and the eriodictyol fraction of vitamin P were tested intravenously, separately and combined, with negative results.

A similar study of the effect of vitamin P therapy on the increased capillary fragility of thrombopenic purpura and rheumatoid arthritis was made, with negative results.

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# INFLUENCE OF RESPIRATION ON BLOOD PRESSURE IN MAN

WITH A NOTE ON VASOMOTOR WAVES

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The study of the influence of respiration on the blood pressure has been based mainly on experiments with animals. Lewis<sup>1</sup> studied in cats the effect on the blood pressure of variations in the pericardial pressure, section of the vagi and differences in the type of respiration and concluded that the main factor was the decrease of the pericardial pressure during inspiration, which caused an increase of the blood pressure in this phase. His experiments on man<sup>2</sup> permitted him to observe the influence of the type and rate of respiration and of the pulse rate. He concluded that the blood pressure has no uniform behavior during the respiratory movement, because it can rise or fall according to the type, frequency and depth of respiration. During quiet breathing no respiratory modifications in arterial pressure were noted.

Visscher, Rupp and Scott<sup>3</sup> made experiments on dogs and came to the conclusion that there is an inspiratory increase of the blood pressure.

Katz and Gauchat<sup>4</sup> studied in animals the factors which contribute to the variations of pulse and blood pressure during deep breathing and ascribed primary importance to changes in pleural pressure.

Mouktar<sup>5</sup> observed an inspiratory fall in the blood pressure of rabbits and an expiratory rise. He obtained the same results with human subjects, by the use of the oscillometer of Pachon.

Hasegawa<sup>6</sup> in 1927 reported the influence of the type of respiration on the blood pressure. He noted an increase during inspiration with thoracic breathing and a decrease during the same phase with abdominal breathing.

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From the Academia Nacional de Medicina, Instituto de Investigaciones Físicas aplicadas a la Patología Humana, Sección Cardiología. This study was aided by a grant from Prospero Baurin.

1 Lewis, T. Studies of the Relationship Between Respiration and Blood Pressure, *J Physiol* **37** 213, 1908.

2 Lewis, T. Studies of the Relationship Between Respiration and Blood Pressure, *J Physiol* **37** 233, 1908.

3 Visscher, M. B., Rupp, A., and Scott, F. H. The Respiratory Wave in Arterial Blood Pressure, *Am J Physiol* **70** 586, 1924.

4 Katz, L. N., and Gauchet, H. W. Observations on Pulses Paradoxus (with Special Reference to Pericardial Effusions). Experimental, *Arch Int Med* **33** 371 (March) 1924.

5 Mouktar, A. Les modifications de la pression artérielle sous l'influence de la respiration chez l'homme, *Bull Acad de méd, Paris* **92** 864, 1924.

6 Hasegawa, U. Influences on Blood Pressure Curves by Volume of Air. *Japan M World* **5** 99, 1925, abstracted, *Arch d mal du cœur* **20** 182, 1927.



On the other hand, the vasomotor waves have been studied also almost exclusively in poisoned or semiasphyxiated animals

Traube<sup>7</sup> experimented on curarized dogs with both vagi cut. Suspension of artificial respiration caused large waves in the arterial pressure which he attributed to rhythmic discharges from the respiratory center toward the vasomotor center.

Hering<sup>8</sup> noticed the same phenomena in dogs under similar conditions. His theory of the mechanism of the changes was identical with Traube's.

Latei, Mayer<sup>9</sup> observed vasomotor waves in anesthetized but not curarized rabbits when respiration was interrupted or retarded. He discovered in his records another type of waves which he called "interference waves." These would be the result of interference of cardiac and respiratory waves.

Starling<sup>10</sup> observed the Traube-Hering waves when he stopped administering artificial respiration to dogs poisoned with morphine or curare. He attributed his results to the increased viscosity of the blood of the vasomotor center. He stated that these waves had also been observed in cases of hemorrhage.

The results of the experiments on animals could not be entirely applied to human beings. On the other hand, the investigations on human subjects were made with unreliable methods, and very contradictory results were obtained by the different authors with regard to the influence of the respiration on the blood pressure.

These reasons have induced us to study this problem by means of registration of the intra-arterial pressure of human subjects. Registration of intra-arterial pressure has been used with human subjects by many workers (von Bonsdorff,<sup>11</sup> Hamilton, Brewer and Brotman,<sup>12</sup> Hamilton, Woodbury and Harper,<sup>13</sup> and others) in order to study other circulatory phenomena not related to respiration.

#### METHOD AND MATERIAL

For the determination of intra-arterial pressure, the Hamilton manometer<sup>12</sup> with a rubber membrane as required for an optical registration was used. The natural frequency of the system was between 60 and 80 oscillations per second. The calibration was made before and after each reading of blood pressure, and the pressure in the system was measured four or five times with a mercury manometer according to the blood pressure of the subject. The respiratory movements were registered simultaneously by means of a pneumograph connected to a Frank segmentary capsule.

These experiments were made on subjects whose cardiorespiratory system was normal and who were in recumbent position. The puncture was made in the humeral, axillary or femoral artery, a needle of 0.7 by 25 gage being used. The time was registered in fifths of a second, with a Jaquet chronometer.

7 Traube, L. *Centralbl f d med Wissensch* **3** 880, 1865, cited by Halliburton<sup>14</sup>

8 Hering, E. *Sitzungsb d k Akad d Wissensch Math-naturw Cl* **60** 829, 1869, cited by Halliburton<sup>14</sup>

9 Mayer, S. *Sitzungsb d k Akad d Wissensch Math-naturw Cl* **74** 281, 1876, cited by Halliburton<sup>14</sup>

10 Starling, E. H. *Principles of Human Physiology*, Philadelphia, Lea & Febiger, 1933

11 von Bonsdorff, B. *Zur Methodik der Blutdruckmessung, mit besonderer Berücksichtigung der Registrierung absoluter Sphygmogramme beim Menschen*, *Acta med Scandinav*, 1932, supp 51, p 1

12 Hamilton, W. F., Brewer, G., and Brotman, I. I Analytical Description of a New High Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intra-Cardiac Pressure, II Pressure Pulse Contours in the Intact Animal, *Am J Physiol* **107** 427, 1934

13 Hamilton, W. F., Woodbury, R. A., and Harper, H. T., Jr. Physiologic Relationships Between Intra-Thoracic, Intraspinal and Arterial Pressures, *J A M A* **107** 853 (Sept 12) 1936

We studied the relations between the blood pressure and the different respiratory types and obtained readings during apnea following deep breathing and apnea following normal expiration. We also studied the effect of the Valsalva test and the influence of coughing.

A total of 15 subjects were studied, and 40 records of intra-arterial pressure were obtained simultaneously with pneumographic records in order to study the respiratory waves. In 27 cases the pressure was taken in the humeral artery, and in 13, in the femoral artery.

Nineteen records were taken during normal breathing, 10 during deep breathing, 7 during deep thoracic breathing and 4 during both slow and fast abdominal breathing. In 4 cases records of intra-arterial pressure were made during the apnea following a deep breath. Six records were made after normal breathing, 2 with the Valsalva test and 5 when the subjects were coughing.

#### RESULTS AND COMMENT

Our investigations in man have permitted us to ascertain that under normal conditions two principal types of waves exist: (1) vasomotor waves that are independent of the respiratory movements and (2) waves coinciding with and depending on respiratory movements.

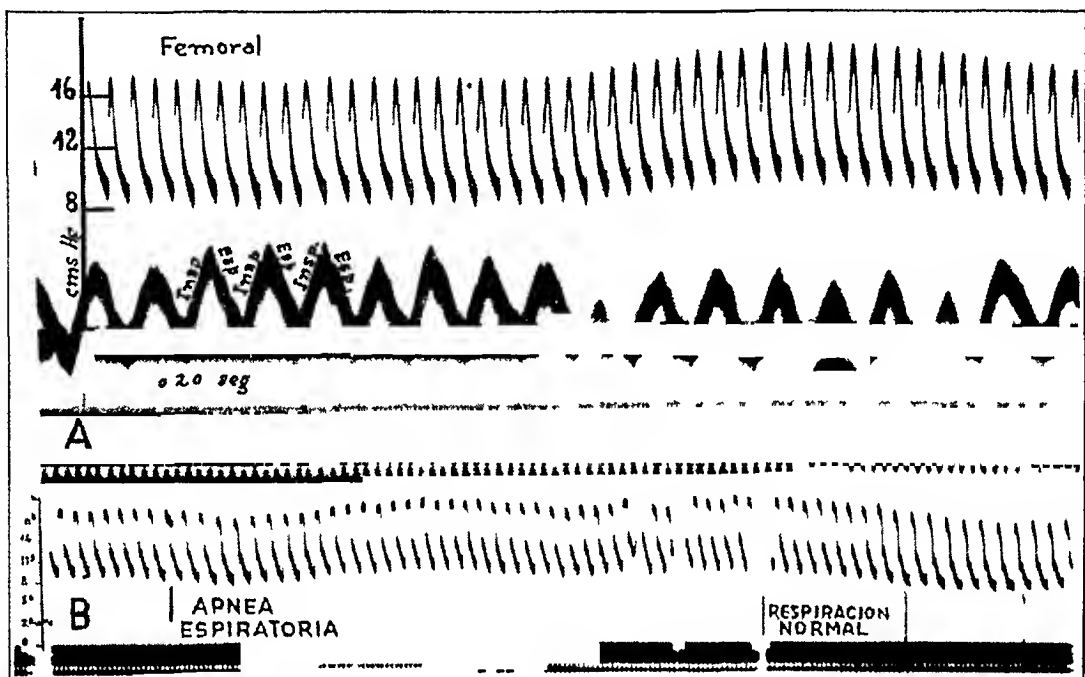


Fig 1—*A*, Traube-Hering vasomotor waves in a normal human subject. The tracing shows spontaneous vasomotor waves independent of respiratory phases. The rate of the waves is about 6 to 7 per minute. *B*, vasomotor waves which are more definite during and after the respiratory pause.

1 The vasomotor waves (Traube-Hering waves) are characterized by their low frequency (6 to 7 per minute) and their independence of respiration. They appear either during normal breathing (fig 1 *A*) or during brief periods of apnea (fig 1 *B*). Under the latter circumstances, the vasomotor waves become clearer and more frequent. They are also more evident when no respiratory variations of the blood pressure are noted. When the curve ascends, the maximal, medial and minimal pressures increase, and when the curve descends, the opposite occurs. The physiologic explanation of these curves is not as yet entirely clear. Possible causes could be:

(a) Rhythmic discharges from the vasomotor centers caused by accumulation of carbon dioxide in the blood. In this connection, Halliburton<sup>14</sup> admitted the

<sup>14</sup> Halliburton, W. D. Traube Waves and Mayer Waves, *Quart J Exper Physiol* 12:227, 1920.

subjection of the vasomotor centers to the same chemical influences as the respiratory centers

(b) Periodic discharges from the respiratory centers on the vasomotor centers (Traube,<sup>7</sup> Aalkjær,<sup>15</sup> Hering<sup>8</sup>) According to this theory, vasomotor waves might be of respiratory origin

(c) Periodic contractions of the arteries caused by reflex action (variation in the sympathetic tone) or chemical stimulation (for instance, by tissular metabolites

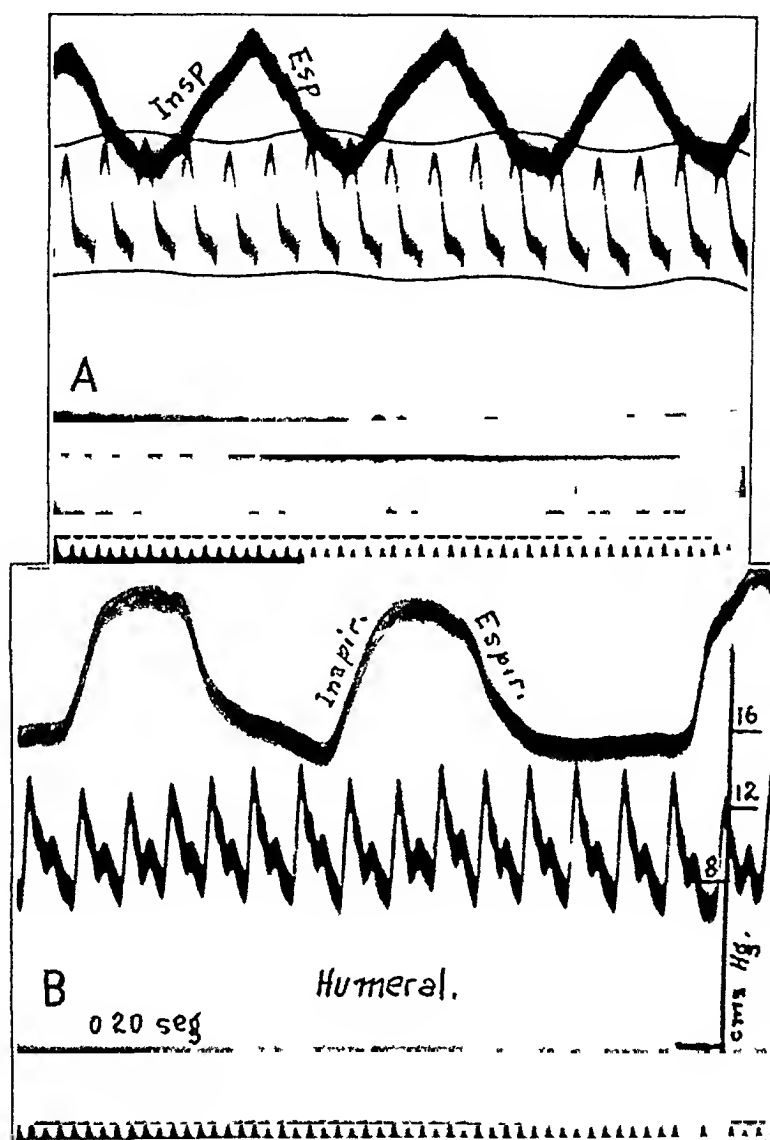


Fig 2—A, variations in blood pressure during ordinary breathing (respiratory waves) There are a fall during inspiration and a rise during expiration without changes in the cardiac rate B, variations of blood pressure during deep, slow thoracic breathing In this case an increase in the blood and the pulse pressure during expiration and the respiratory pauses may be noted

and cholinergic or adrenergic substances) The respiratory and vasomotor centers are not involved

15 Aalkjær, V Ueber Aussehen, Bildungsstelle und Ursache der Traube-Hering-Mayerschen-Blutdruckschwankungen, Skandinav Arch f Physiol 71 301, 1935

On suspension of respiration, Traube-Hering waves become clearer. Therefore, it is probable that they have a central origin and that the vasomotor centers are excited from the respiratory centers or by the tensional variation of the oxygen and carbon dioxide in the blood (hypoxemia and hypercapnemia). According to Halliburton<sup>11</sup> these would be the true vasomotor waves to which the name of Traube, their discoverer, should be given.

2 Respiratory waves are characterized by a rhythm synchronous with that of respiration.

The influence of the respiratory type, thoracic or abdominal, and the depth and velocity of the respiratory movements on the blood pressure were studied.

In 7 subjects no respiratory modifications were observed during ordinary breathing. An increase in the systolic and diastolic pressure during expiration

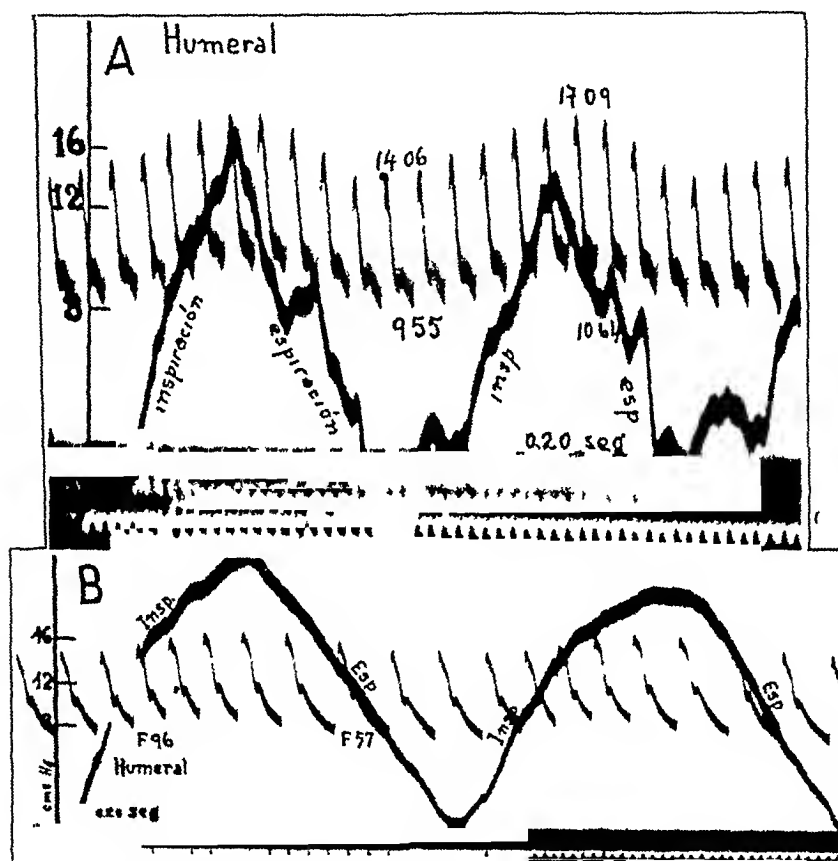


Fig 3—A, variations in the blood pressure during deep, slow thoracic breathing. This tracing shows a progressive rise in blood pressure (systolic and diastolic) during inspiration. The highest point is reached at the end of the inspiratory phase and the beginning of expiration. During expiration a fall of both pressures is seen. There are significant variations in pulse pressure. B, variations of blood pressure and cardiac rate during deep, slow thoracic breathing. A rise during inspiration, with tachycardia, and a drop during expiration, with bradycardia, are recorded.

was observed in 9, and a fall of the blood pressure during the same phase was noted in 3. The opposite occurred in inspiration, the rise of arterial pressure generally started at the beginning of expiration. The pulse pressure was increased with expiration in 6 subjects. In 10 an expiratory bradycardia was noted, and in the remainder there were no variations in the heart rate.

With deep breathing an expiratory increase was recorded in 8 tracings and an inspiratory rise in 2, in 7 the pulse pressure increased during expiration and in 2 during inspiration.

With deep thoracic breathing, an increase in pressure during expiration and a decrease during inspiration were recorded in 5 tracings. In 2 other tracings the pressure increased during inspiration, the pulse pressure rose during expiration in 4 and during inspiration in 1. Expiratory bradycardia was registered in 6.

In 2 cases we observed an inspiratory elevation during deep, slow abdominal breathing, with an increase in the pulse pressure in 1 case and in the other a fall, there was expiratory bradycardia in both. The rise began in 1 case in the middle and in the other at the very beginning of inspiration (the humeral artery

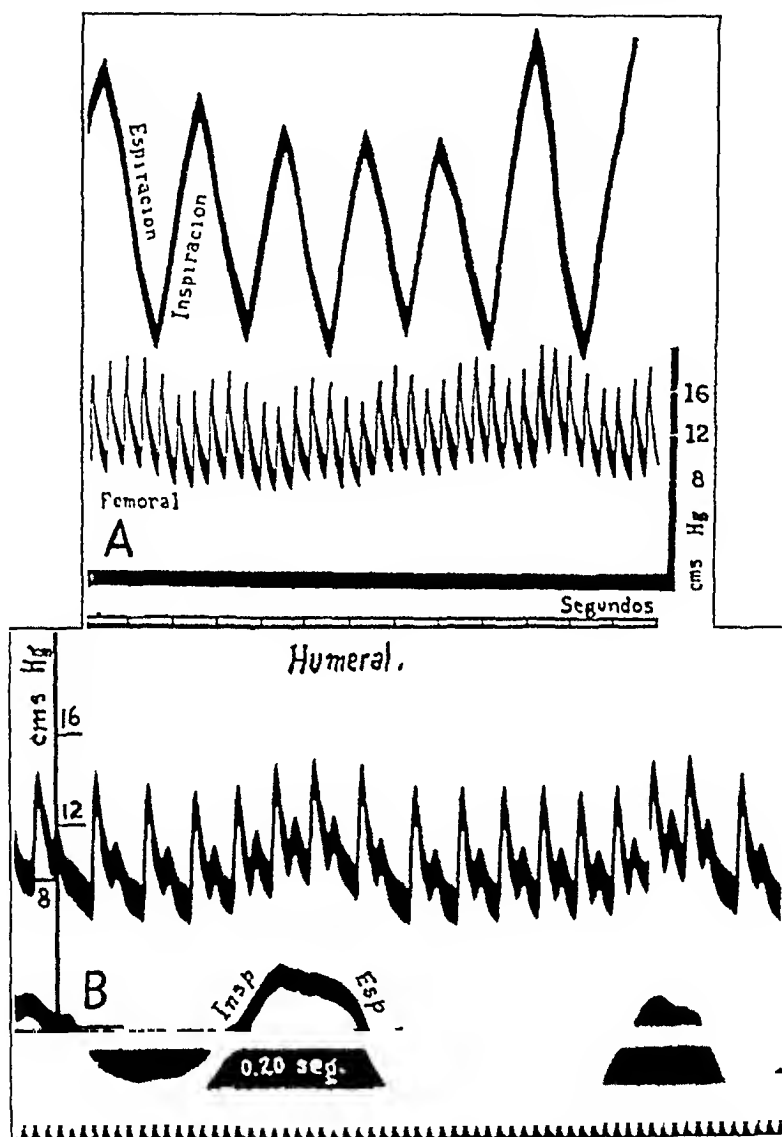


Fig 4—A, variations of blood pressure during deep, fast thoracic breathing. Blood pressure falls at the beginning of inspiration and rises at the end. B, variations of blood pressure during slow, deep abdominal breathing. This tracing shows a rise of the arterial pressure during inspiration and a fall during expiration. The fall in diastolic pressure and the consequent increase in pulse pressure are especially apparent.

was used for both). When without withdrawing the needle from the artery we told 1 of these patients to change the breathing from abdominal to thoracic, it was clearly registered that the blood pressure fell during inspiration.

In the same patients, when the rate of breathing was increased (by deep and fast abdominal movements), a fall of blood pressure during inspiration was

observed in 1, and in the other, even when the pressure rose on inspiration, the amplitude of the variations of arterial pressure diminished noticeably

Among the many factors supposed to have a part in the production of respiratory waves, the changes which the intrapleural and the abdominal pressure undergo are worthy of consideration.

The negative pressure within the pleura is greater during inspiration than during expiration. During ordinary inspiration, a larger quantity of venous blood goes to the heart, because of the greater negative pressure within the thorax. At the same time, with the descent of the diaphragm, the abdominal pressure is increased. Both factors contribute to augment the inflow of blood to the heart at the end of inspiration. The result is an increase in the cardiac output in this phase.

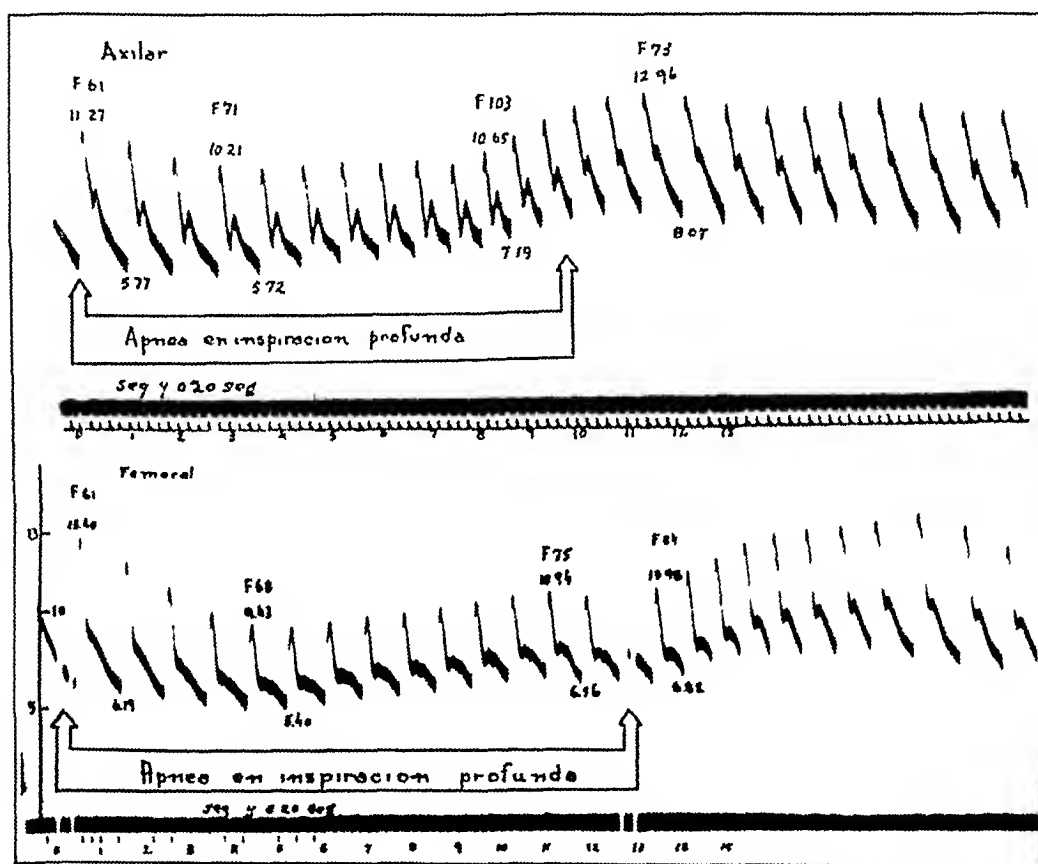


Fig 5—Inspiratory apnea. Variations in the blood pressure, in the shape of the pressure curve, in the pulse pressure and in the cardiac rate are clearly apparent. The decrease in pulse pressure and the exaggeration in the dicrotism are most evident.

During expiration, the phenomena are reversed, and there is a consequent diminution in the blood pressure.

We must still consider other factors, the intervention of which can alter the results stated above. We shall mention the anatomicophysiological condition of the pulmonary bed, the variations in the diameter of the pulmonary blood vessels and the resistance which these vessels offer to the blood. The intrapericardial pressure is also significant.

During inspiration, especially at the beginning, the pulmonary bed admits a greater quantity of blood through expansion of the lung (Heimbecker<sup>16</sup> and

16 Heimbecker, P. The Mechanism of the Respiratory Waves in Systemic Arterial Blood Pressure, *Am J Physiol* 81:170, 1927.

Trimby and Nicholson<sup>17</sup>) Consequently, the resistance to the blood in its pulmonary course and the inflow of blood to the left ventricle are lessened and the blood pressure tends to decrease

In expiration, in spite of greater resistance of the pulmonary vessels, the blood flows more easily into the left auricle The consequence of this is an increase in the systemic blood pressure Furthermore, during inspiration there is a decrease in the intrapericardial pressure (Lewis<sup>1</sup>) with an increase in the diastolic inflow and the cardiac output

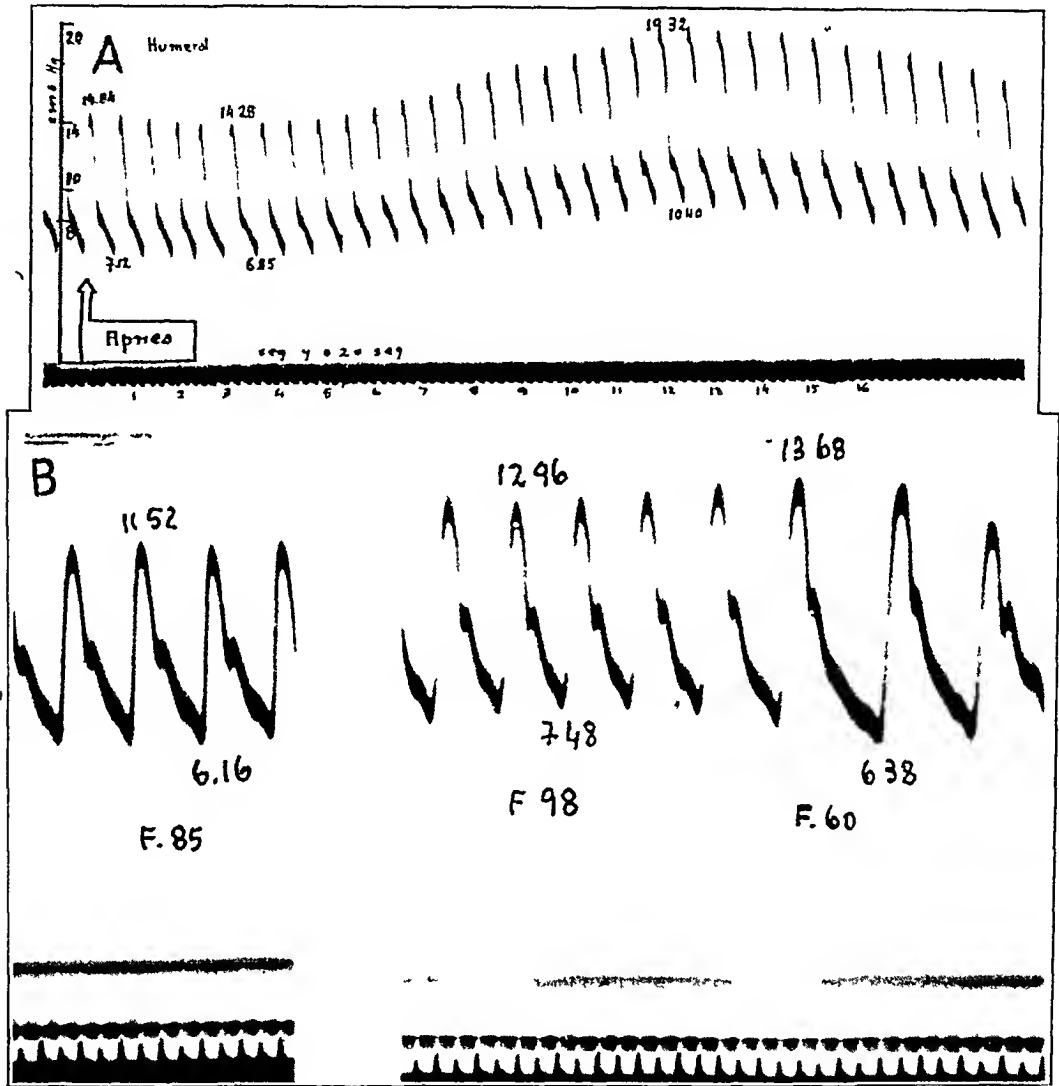


Fig 6—A, expiratory apnea After a slight fall of pressure a continuous elevation of the systolic and the diastolic blood pressure and an increase of pulse pressure are noted B, this tracing shows a rise of systolic and a fall of diastolic blood pressure, associated with an increase of the pulse pressure and bradycardia The tracing was made at the time of the diaphragmatic and abdominal contractions which followed expiratory apnea

The relationship between all these factors may explain the fluctuations of blood pressure in the course of normal breathing In the following table we consider the different factors which act on the blood pressure

With ordinary breathing there are generally, as we have stated, an inspiratory fall and an expiratory elevation of the blood pressure (fig 2 A) The vascular

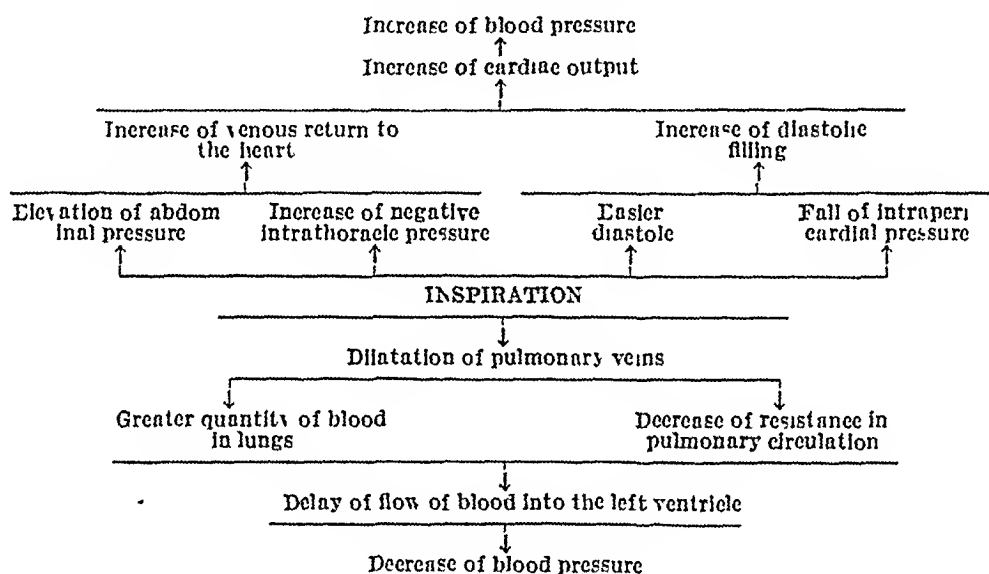
17 Trimby, R H, and Nicholson, H C Some Observations on the Nature of the Respiratory Waves in Arterial Blood Pressure, *Am J Physiol* 129 289, 1940

capacity of the lung probably predominates over the thoracic-abdominal factor in these cases

During deep, slow thoracic breathing, the variations of the blood pressure are clearer than during ordinary breathing. As has been previously stated, there are generally a fall in pulse rate and blood pressure during inspiration and a rise during expiration and the respiratory pause (fig 2 B). The behavior of the blood pressure is neither constant nor uniform, as we have found cases in which it has risen during inspiration (fig 3 A). These variations are independent of the heart rate. We generally found expiratory bradycardia (fig 3 B), which commenced sometimes at the beginning and sometimes at the end of expiration and persisted during the respiratory pause.

An increase in blood pressure during inspiration is probably due to predominance of the factor of negative intrathoracic and positive abdominal pressure.

#### *Factors Which Contribute to Variations of Blood Pressure During Inspiration*



This predominance favors the venous return to the heart and hence the systolic discharge of the ventricle. An increase in blood pressure during expiration leads one to suppose the predominance of the pulmonary factor, with a consequent increase in the venous return to the heart.

During deep, fast thoracic breathing an increase of the blood pressure during expiration was observed (fig 4 A), and with deep, slow abdominal breathing there was a rise of blood pressure during inspiration (fig 4 B).

*Blood Pressure During Inspiratory Apnea*—The record of the arterial pressure curve during apnea following a deep inspiration shows that both the systolic and the diastolic pressure fall gradually in the first three to five seconds, and the dicrotism becomes more evident (fig 5). The cardiac rate increases 6 or 7 beats per minute. The initial fall is followed by a gradual rise of the arterial curve and the cardiac rate until the end of the apnea. As soon as breathing is recommenced, the arterial curve regains its original state and the blood pressure returns to its original level, though during a few seconds it may be higher. These variations may even be recorded in arteries far from the thorax, e. g., in the posterior tibial artery.



The changes in the first seconds of the period of apnea may be explained on the basis of mechanical interference, chiefly blocking of the venous return to the heart, which tends to reduce the amount of blood flowing to the heart and produces diminution of the cardiac discharge

The changes of the second phase may be explained by the intervention of reflex phenomena due to stimulation of vasomotor centers by the hypercapnemia or hypoxemia associated with any more or less prolonged respiratory pause

*Arterial Pressure During Expiratory Apnea*—In the course of the interval of apnea following an ordinary expiration, it is observed that after a slight decrease in blood pressure during the first seconds there is a progressive increase in the maximal, the medial and the minimal pressure until the end of the test, which

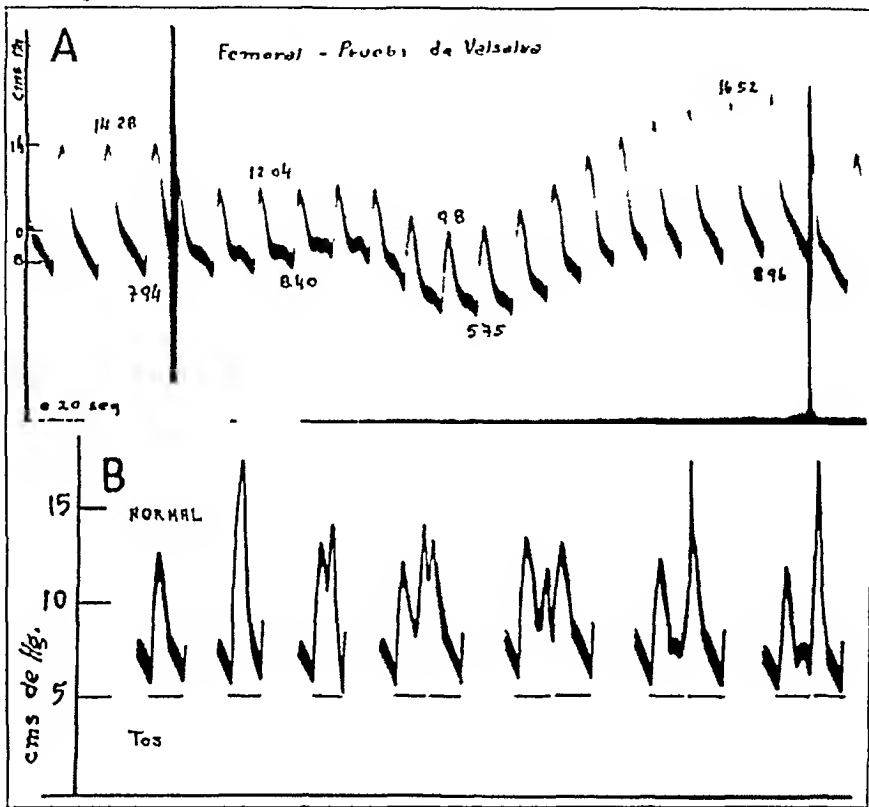


Fig 7—A, Valsalva test Three phases are apparent In the first two there is a definite fall of pulse and blood pressures The fall in blood pressure is especially apparent in the second phase (empty pulse) In the third phase the pulse pressure definitely increases (full pulse) B, diagram showing the effects of the exertion of coughing on the intra-arterial pressure Note the sudden rise of pressure caused by coughing and coincident with the different gradients of the pulse

generally lasts from fourteen to twenty seconds The pulse pressure also increases toward the end (fig 6 A) Holding the breath for a longer period causes a series of muscular and diaphragmatic contractions with a terminal elevation of the arterial pressure and a slowing of the pulse (fig 6 B)

The initial descent could be interpreted as the result of stopping the respiratory movements The consequent elimination of the thoracic-diaphragmatic factor reduces the venous flow to the heart and diminishes the cardiac output The subsequent rise could be explained by the excitation of the vasomotor centers caused by oxygen hyposaturation of the arterial blood (hypoxemia) or by accumulation of carbon dioxide (hypercapnemia) The cardiac rate increases slightly

as a result of the sympathetic stimulation. If the test is prolonged muscular contraction produces abrupt changes in intrathoracic pressure.

*Valsalva Test*—The curves of the arterial pressure during the Valsalva test (expiratory effort with the glottis closed) show some similarity to those of inspiratory apnea. Three phases are noticeable (fig 7 A).

1 The systolic pressure falls, the diastolic pressure rises, and a slight acceleration of the heart beat occurs. The pulse pressure diminishes, producing what is called by Hamilton and his associates "empty pulse". The decrease in the systolic pressure may be explained by the blocking of the venous return to the heart. The elevation of the diastolic pressure and the tachycardia may be due to a reflex originating in the carotid sinus (Hamilton, Woodbury and Harper<sup>13</sup>).

2 In the second phase there is a characteristic descent of both the systolic and the diastolic pressure. Hamilton and his associates, by measuring the intrathoracic and blood pressures simultaneously, have proved that during this phase the arterial pressure drops abruptly to the level known as "net" blood pressure. The value for the latter is obtained by subtracting the intrathoracic pressure from the arterial pressure.

3 When the strain is released, the pulse curve becomes characteristic of the type known as "full pulse", the systolic and the diastolic pressure rise and surpass the level previous to the test and the cardiac rate becomes slower. These variations are interpreted as being caused by the abrupt flow of blood to the thorax and by reflexes originating in the cardioaortic region (Hamilton, Woodbury and Harper<sup>13</sup>).

*Effect of Cough on Arterial Pressure*—The intra-arterial pressure was studied during the exertion of coughing, and it was found that it rose sometimes to very high levels. When the cough coincides with the top of the pulse curve, the systolic pressure may duplicate its normal values (fig 7 B).

The influence which this phenomenon has on the cerebral arteries has been studied by Hamilton, Woodbury and Harper<sup>13</sup>. The simultaneous registration of intra-arterial, intrathoracic and intraspinal pressure has shown that an abrupt rise of intra-arterial pressure caused by coughing is accompanied by an increase in intraspinal pressure. Therefore, a rise in the intra-arterial pressure in the brain is accompanied by a correlative increase in the pressure of the cerebrospinal fluid, and possible rupture of an artery is avoided. They have proved that identical protecting mechanisms against abrupt rises in blood pressure exist in the thorax and in the abdomen.

#### SUMMARY AND CONCLUSIONS

The influence of breathing, inspiratory and expiratory apnea, the Valsalva test and coughing on the intra-arterial pressure in man was studied.

Two types of waves were found: (a) vasomotor waves, which are independent of the respiratory movements and should be called by the names of their discoverers, Traube and Hering, and (b) blood pressure waves depending on the respiratory movements (respiratory waves).

The different factors which influence the production of these waves have been commented on.

The intra-arterial pressure has no uniform or fixed behavior during the respiratory movements but may rise or fall in accordance with the type of breathing—thoracic or abdominal—or with the frequency or depth of respiration. Even

during ordinary breathing, slight changes are noticeable, the most constant being a fall of blood pressure during inspiration and an elevation during expiration. With deep, slow thoracic breathing there usually occur an inspiratory fall and an expiratory rise of the blood pressure. The opposite, as a rule, is true of abdominal breathing of the same type.

Curves of intra-arterial pressure registered during inspiratory apnea and the Valsalva test show a definite fall of blood pressure at the beginning, while those taken during expiratory apnea are characterized by a slight initial fall and a terminal rise. Coughing causes great increase in the blood pressure.

Professor Gonzalo Bosch and Dr. Enrique Mo. Gatti gave us permission to conduct our investigations in the Hospicio de las Mercedes. Dr. Eduardo Braun-Menendez offered suggestions and criticisms.

Viamonte 1519

# RATE OF SEDIMENTATION OF ERYTHROCYTES IN SICKLE CELL ANEMIA

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Since the original description of sickle cell anemia, by Herrick<sup>1</sup> in 1910, much has been written about this disease with little attention given to the problem of the sedimentation of the erythrocytes. A review of the literature since 1935 revealed 65 publications on sickle cell anemia. These articles contained 248 reports of cases, 149 being fairly detailed. In only 37 of these reports was the sedimentation rate mentioned. In 9 of the 37 the method used was not indicated, and in 24 there was no mention of the degree of anemia. Although these data are difficult to interpret, it would appear that in 7 instances the sedimentation rate was slow. Diggs<sup>2</sup> recorded the sedimentation rate in 27 of a series of 37 cases and found it to be slow in many instances. He noted a decided variation even in the same subject. No attempt was made to explain these findings. Bunting<sup>3</sup> in an in vitro study of the bloods of 4 patients with active sickle cell anemia and 1 with the "trait" found the sedimentation rate to be directly proportional to the degree of moulage formation.

A review of the records of patients admitted (total, 287,257, Negro, 131,775) to Charity Hospital during the past five years (January 1937 to January 1942) showed 40 instances of active sickle cell anemia. In only 4 was the sedimentation rate recorded, and in all these it was slow. In addition, the relatively few data on the sedimentation rate reported before 1935 offer little information, since methods for its determination were not standardized at that time.

Because of the lack of information on the sedimentation rate in sickle cell anemia, the value of this procedure in clinical diagnosis and the frequency of sickle cell anemia in the Negro race

(Diggs stated that it is the most commonly encountered primary blood dyscrasia in Negroes), a study was undertaken to evaluate some of the factors influencing the rate of sedimentation of the erythrocytes. An effort was made to standardize the procedure for cases of this disease in order that the previously reported variabilities of values might be controlled.

## GENERAL METHOD OF STUDY

These observations comprise data collected in repeated studies of 15 patients with active sickle cell anemia and 14 controls. The subjects chosen as controls had blood pictures that varied from the normal to ones similar, except for sickling, to those encountered in the patients with sickle cell anemia. Six of them had anemia (due to various causes) other than sickle cell anemia. The 14 diseased control subjects had the following clinical states: diabetes mellitus, disseminated lupus erythematosus, benign hypertensive cardiac disease, tuberculous peritonitis, syphilitic heart disease, bleeding peptic ulcer and acute gastritis, pulmonary tuberculosis (2 subjects) and pernicious anemia (2 subjects). Three of the control subjects were normal. The details of the blood pictures of all of the patients with sickle cell anemia used in these studies are summarized in table 1. These patients were carefully studied in order to make certain that they were free from any complicating disease.

The blood was collected in a uniform manner as follows. The patient rested for fifteen minutes before the blood was drawn. A blood pressure cuff was used as a tourniquet and inflated to a pressure slightly above the diastolic. About 10 cc of blood was removed from the antecubital vein, the entire procedure requiring not more than sixty seconds. Nine and five-tenths cubic centimeters of the blood was transferred immediately to a 10 cc vial containing 8 mg of dry potassium oxalate and 12 mg of ammonium oxalate. The vial was immediately corked and gently rotated. The blood was placed in the sedimentation tubes within five minutes and the rate of settling measured by the method of Wintrobe<sup>4</sup>. When corrections for anemia were necessary the correction values of Wintrobe<sup>4</sup> were used. After this initial determination of the rate of sedimentation was completed, the volume of packed red cells was measured by centrifuging the hematocrit tube for thirty minutes at 3,000 revolutions per minute. Occasionally an additional ten minutes of centrifugation was done in order to make certain of complete packing, and in no instance was further packing noted.

In addition to these routine procedures other groups of studies to be described, were carried out to observe the influence of several factors on the rate of sedimentation.

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1 Herrick, J B. Peculiar Elongated and Sickle Shaped Red Blood Corpuscles in a Case of Severe Anemia, *Arch Int Med* 6 517-521 (Nov) 1910.

2 Diggs, L W, and Bibb, J. The Erythrocyte in Sickle Cell Anemia, *J A M A* 112 695-700 (Feb 25) 1939.

3 Bunting, H. Sedimentation Rates of Sickled and Non-Sickled Cells from Patients with Sickle Cell Anemia, *Am J M Sc* 198 191-193, 1939.

4 Wintrobe, M M, and Landsberg, J W. A Standardized Technique for the Blood Sedimentation Test, *Am J M Sc* 189 102-114, 1935.

RELATION BETWEEN DEGREE OF ANEMIA  
AND SEDIMENTATION RATE

In order to learn the variations in the sedimentation rate with the degree of anemia in patients with sickle cell anemia, the bloods of 10 patients with active sickle cell anemia were observed, the sedimentation rates being determined as just outlined and the results correlated with the degree of anemia expressed as packed cell volume

*Results*—The sedimentation rates for the 10 patients, after correction by use of the Wintrobe chart, are summarized in figure 1 The 6 patients with the most severe anemia, all with packed cell volumes of less than 25 per cent, had rates which were slower than one would predict for the anemia The 4 patients with less severe anemia, who had packed cell volumes greater

to evaluate this influence, or that of any of the chemical constituents of the serum, on the sedimentation rate, all reports encountered in the literature cited normal values for plasma proteins in patients with uncomplicated sickle cell anemia<sup>5</sup> In 4 of 40 cases from Charity Hospital the values for total plasma proteins were normal These constituents were not studied in the others The blood cholesterol has been recorded in the literature as approximately normal in 6 patients<sup>6</sup>

It is interesting that even when the erythrocytes were allowed to settle for as long as four days they did not fall the distance that they normally do in one hour To our knowledge, this has not been described as associated with any other type of anemia A persistently retarded sedimentation rate is sometimes seen in

TABLE 1—Details Concerning the Blood of the Fifteen Patients with Sickle Cell Anemia Used in the Experiments

Subject No	Sex	Age, Years	Red Blood Cell Count, Millions	White Blood Cell Count, Thousands	Hemo globin (New comber), Gm per 100 Cc	Hemato crit Read ing, %	Sedimen tation Rate (Win trobe), Mm per Hr	Mean Corpus cular Volume, Cubic Microns	Mean Cor puscular Hemo globin, Micro grams	Mean Cor puscular Hemo globin Concen tration, %	Differential Leukocyte Count, per Cent			
											P	L	M	E
1	F	8	3.13	11.4	9.6	20	20	92.6	30.6	33.1	67	22	6	4
2	F	8	2.2	35.0	6.6	20	21	90.9	30.0	33.0	85	12	3	0
3	M	16	1.9	10.2		14	24	93.3			70	23	4	1
4	M	20			9.0	31	11			30.6				
5	M	15	2.7	12.8	6.5	25	5	92.5	24.0	26.0	59	25	3	2
6	F	23	2.3	18.9	7.1	21	10	91.3	31.7	34.7	73	22	5	0
7	M	37	1.4	6.9		16	45				49	51	2	0
8	M	7	2.7	14.0	7.3	19	15	70.3	27.0	38.4	68	21	8	3
9	M	18	2.8	27.7	7.0	21	17	75.0	25.0	33.3	66	27	5	1
10	F	13	2.8	12.6	7.8	27	2	96.4	27.8	28.8	59	32	8	1
11	F	26	2.5	8.4	9.1	21	1.5	98.2	37.2	28.5	51	34	5	8
12	F	5	3.8	25.7	10.0	35	16	92.1	26.3	26.3				
13	F	38				38	10							
14	M	14	2.1	21.0	6.5	19	6	90.4	30.0	30.9				
15	F	7	2.3	24.0	7.2	21	7	91.1	31.3	34.2	70	22	5	3

than 25 per cent, had sedimentation rates which were within the expected range The erythrocytes of 4 of the 6 patients with severe anemia did not settle the calculated normal distance even though they were allowed to remain undisturbed in the tubes for four days

*Comment*—These observations suggest that in sickle cell anemia factors exist which tend to retard the rate of sedimentation of the erythrocytes and may be related to the degree of anemia Since all of the patients except patient 9 had a normochromic, normocytic anemia, it is unlikely that the slow settling is related to the volume of the erythrocytes or to the amount of hemoglobin packed into each one Since the degree of sickling is more or less directly proportional to the degree of anemia, it is possible that the abnormal shape of the erythrocyte may influence the rate of sedimentation This factor will be discussed later No published data were encountered concerning effects of the blood serum on the sedimentation rate in sickle cell anemia Although no attempts were made in these studies

polycythemia vera and in severe dehydration In these two states the erythrocytes are absolutely and relatively increased

The results of this group of experiments indicate the lack of reliability of the Wintrobe correction chart for correcting for the degree of anemia Wintrobe<sup>4</sup> apparently did not test his correction chart with the bloods of persons with sickle cell anemia

In order to study the effects of relative volumes of erythrocytes and serum on the sedimentation rate in sickle cell anemia, the next group of experiments was conducted

5 Cooke, J, and Keller, M Sickle Cell Anemia in a White Family, J Pediat 5 601-607, 1934  
6 Vryonius, G Studies of the Effect of Intravenous Administration of Liver Extract in Patients with Sickle Cell Anemia, J Lab & Clin Med 26 1470-1473, 1941  
Chediak, M, Cabrera Calderin, J, and Prado y Vargas, G Sickle Cell Anemia in Cuba, Arch de med int 5 313-370, 1939  
Cabrera Calderin, J G, Labourdette Scull, J M, and Prado y Vargas, G Dos casos de anemia a hematias falciformes, Bol Soc cubana de pediat 9 179-206, 1937

# RELATION OF SEDIMENTATION TO VARIOUS DEGREES OF ANEMIA, ARTIFICIALLY PRODUCED

Four of the 10 patients used in the previous experiment were employed for these studies. Two were from the group of 6 with severe anemia and slow sedimentation rates, and the

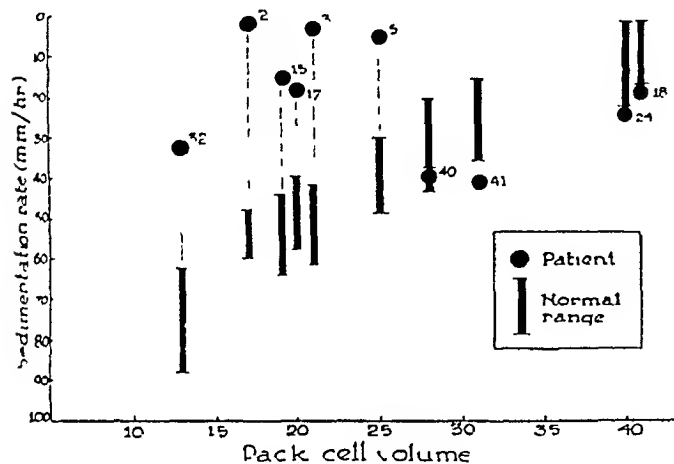


Fig 1—The relation between the degree of anemia and the sedimentation rates of 10 patients with sickle cell anemia

other 2 were from the group of 4 with moderate anemia and sedimentation rates that were within the expected range for the degree of anemia. The erythrocytes and plasma were separated and recombined in different proportions so that various degrees of artificial anemia were produced. The sedimentation rates were determined for each combination.

**Results**—The results are summarized in figure 2. It can be seen that the sedimentation rate increased as the artificially produced anemia increased. However, the sedimentation rate remained slower than that predicted from the Wintrobe chart, regardless of the degree of artificial anemia, in the patients with the severe anemia and relatively slow rates (fig 2A). In the patients with moderate anemia and sedimentation rates that were already within the expected range for this anemia, the erythrocyte sedimentation rate likewise remained within the calculated range regardless of the degree of anemia artificially produced (fig 2B).

**Comment**—Artificially produced anemia will not produce a relative retardation of the sedimentation rate. In the first experiments it was found that in the cases of more severe anemia with packed cell volumes of less than 25 per cent, the sedimentation rate was retarded out of proportion to the degree of anemia. In those studies only naturally occurring anemia was correlated with the sedimentation rate. In the latter group of studies the results indicate that

it is not the degree of packed cell volume per se that is responsible for the retardation of the sedimentation, for when the anemia was varied artificially the sedimentation rate varied as would be expected from Wintrobe's correction charts. Therefore, it must be something else related to the degree of anemia, not the anemia per se, which tends to retard sedimentation. This suggests in vivo rather than in vitro phenomena. Since the sedimentation rate is not directly related to the concentration of the erythrocytes, it was then considered advisable to study the relationship of rouleau formation in sickle cell anemia and the sedimentation rate. It is appropriate for the sake of continuity of thought, to describe first observations on the effects of oxygen and carbon dioxide on sedimentation.

## OXYGEN AND CARBON DIOXIDE AND THE SEDIMENTATION RATE

The effect of oxygen and carbon dioxide on the sedimentation rate was studied for 4

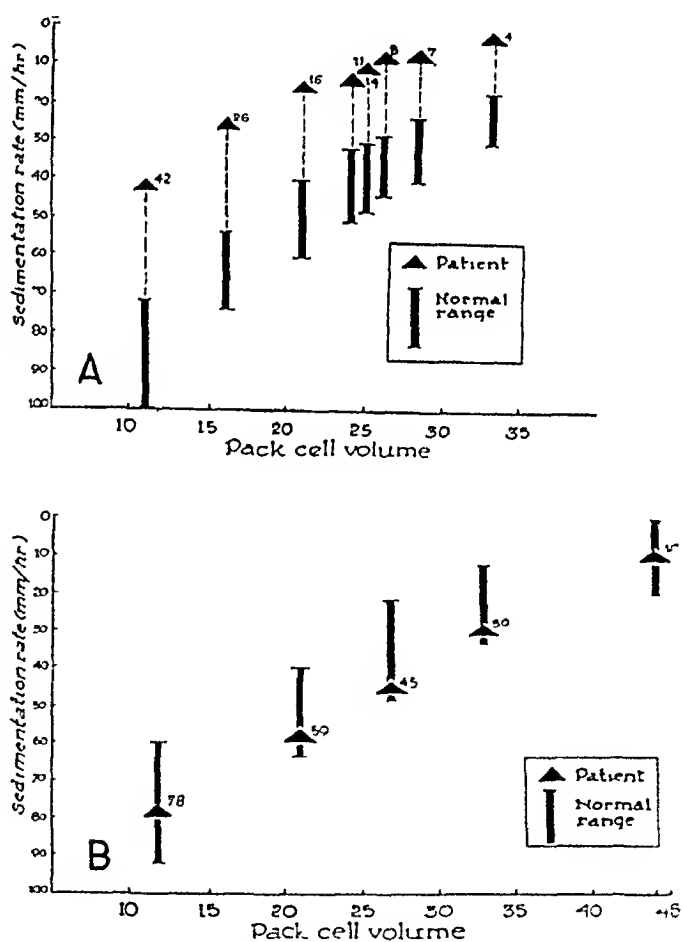


Fig 2—A, the effect of artificial anemia on the sedimentation rate of a patient in whom the degree of anemia was severe, the packed cell volume being less than 25 per cent. B, the effect of artificial anemia on the sedimentation rate of a patient in whom the degree of anemia was moderate, the packed cell volume being greater than 25 per cent.

patients with sickle cell anemia and 4 control patients with conditions other than sickle cell anemia. Fifteen cubic centimeters of oxylated blood from each of the patients was divided into

three portions, each being placed in a 50 cc Erlenmeyer flask containing air, approximately 100 per cent oxygen and approximately 100 per cent carbon dioxide, respectively. The sedimentation rate from the flask containing air was determined immediately. The remaining flasks

hour. The effects in the control group were not nearly so marked.

The sedimentation rates of the bloods subjected to a negative pressure slightly greater than atmospheric, 780 mm of mercury, for twenty-three minutes showed alterations similar to those produced by saturation with oxygen, although the bloods appeared grossly identical in color to those completely saturated with carbon dioxide (table 2). When the vacuum-treated blood was saturated with carbon dioxide, the sedimentation rate was reduced to almost zero, and when it was saturated with oxygen the rate was greatly accelerated.

*Comment*—The mechanism by which carbon dioxide and oxygen produce the changes in sedimentation rate is unknown. Bunting<sup>3</sup> noted a similar effect and stated that oxygen tended to favor rouleau formation and decrease sickling while carbon dioxide had an opposite effect. Such morphologic changes were lacking in the control bloods. The relations of these phenomena are further discussed in the next group of experiments. Carbon dioxide has been known to increase the volume of the erythrocytes, inducing an exchange of electrolytes between the erythrocytes and the plasma, to change the *p<sub>H</sub>* of the plasma and cells, etc.<sup>7</sup> The relative importance of these changes with regard to the sedimentation rate in normal and in diseased patients is not clear. The fact that the sedimentation rate

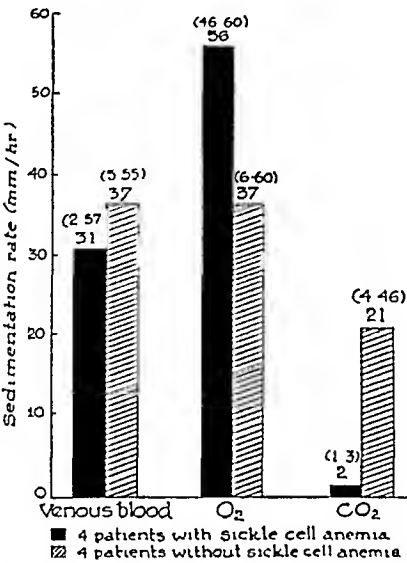


Fig 3—The effect of oxygen and carbon dioxide on the sedimentation rates of patients with sickle cell anemia and patients with other conditions.

were corked and were rotated occasionally for sixty minutes, after which the sedimentation rates were determined. The bloods of a patient with sickle cell anemia and a control were tested simultaneously.

TABLE 2—Influence of a Vacuum on the Sedimentation Rates of Three Patients with Sickle Cell Anemia and Four Control Subjects

Sickle Cell Anemia, Sedimentation Rate, Mm per Hr				Control Sedimentation Rate Mm per Hr				
Venous Blood	Vacuum 23 Minutes, 780 Mm Hg	Oxygen	Carbon Dioxide	Diagnosis	Venous Blood	Vacuum 23 Minutes, 780 Mm Hg	Oxygen	Carbon Dioxide
31	35	63	1	Malnutrition	34	30	31	23
7	33	67	0	Pregnant, anemia	60	60	61	60
8	12	46	1	Normal	32	30	38	24
				Pyelitis	58	57		

The bloods of 3 patients with sickle cell anemia and 4 control patients were subjected to a negative pressure of 780 mm of mercury for twenty-three minutes, and the sedimentation rates were determined and compared with those previously found for the same bloods.

*Results*—Oxygen invariably accelerated the sedimentation rates of the patients with sickle cell anemia, but did not accelerate the rates of the control patients. Carbon dioxide greatly retarded the sedimentation rates of the patients with sickle cell anemia and slightly retarded the settling rates of the control group (fig 3). In fact, carbon dioxide almost entirely stopped the settling of the erythrocytes of the persons with sickle cell anemia, reducing it to 1 to 3 mm in an

was accelerated by the removal of oxygen, carbon dioxide and other gases by vacuum, an effect similar to that produced by saturation of the blood with oxygen, tends to indicate that it was the removal of the carbon dioxide that produced this effect. The blood had the dark color of reduced hemoglobin. An addition of oxygen further accelerated the rate of sedimentation, while an addition of carbon dioxide reduced the rate to almost zero. It is possible that addition of oxygen to the blood of persons with sickle cell anemia produces its effect by

7 Ham, H. T., and Curtis, F. C. Sedimentation Rate of Erythrocytes, *Medicine* 17:447-517, 1938.  
Fahraeus, R. Suspension Stability of the Blood, *Physiol Rev* 9:241-274, 1929.

decreasing the relative amounts of carbon dioxide

#### ROULEAU FORMATION AND THE SEDIMENTATION RATE

The relationship of rouleau formation and the sedimentation rate was studied in 5 patients with

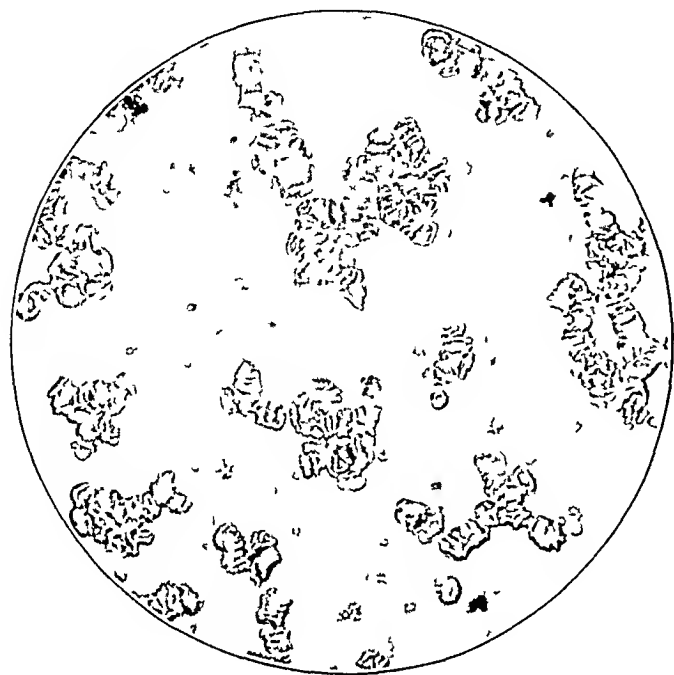


Fig 4—Rouleaux as seen immediately after removal of venous blood from the antecubital vein. These were of an "abnormal" character and resembled agglutination because of the more or less haphazard clumping.

severe sickle cell anemia. Five patients with conditions other than sickle cell anemia were used as control subjects. Immediately after the blood had been collected as previously described, a drop was placed on a slide under a cover slip and sealed in with petrolatum. About 5 cc of the remaining blood was placed in each of two 50 cc Erlenmeyer flasks. One flask was already filled with oxygen and the other with carbon dioxide. Each was rotated occasionally over a period of about sixty minutes in order to insure saturation of the contained blood with the respective gases. A wet preparation was made with a drop from each of the flasks, as previously described for the venous blood, and rouleau formation was observed. At the time each of the preparations was made for study of rouleau formation, a preparation for determination of the sedimentation rate was set up and the rate determined.

**Results**—In the bloods of the 5 control patients normal rouleau formation was seen. On the other hand, the bloods from the patients with sickle cell anemia showed at least three different types of phenomena, depending on whether or not they were saturated with oxygen or carbon dioxide or were merely venous blood.

1 The erythrocytes of venous blood congregated to form rouleaux of an "abnormal" type. These rouleaux were imperfect in that the erythrocytes were not stacked neatly but were gathered in irregular masses resembling agglutination rather than rouleaux (fig 4). Pressure on the cover slip dispersed the rouleaux and separated the cells momentarily. After three to five minutes the cells reunited in their "abnormal" formation. When the erythrocytes were dispersed they showed signs of early sickling.

2 The blood that was saturated with carbon dioxide showed no evidence of rouleau formation, not even a tendency of the erythrocytes to aggregate. There was marked sickling (fig 5).

3 The blood saturated with oxygen showed rouleau formation that appeared to be normal in every respect (fig 6).

The rate of sedimentation showed a definite correlation with rouleau formation (fig 7). The venous blood which showed the "abnormal" rouleaux had a mean sedimentation rate of 21 mm in one hour. The blood saturated with carbon dioxide, which showed no rouleaux, had an average rate of 2 mm while the blood saturated with oxygen, which showed normal rouleaux, had a rate of 48 mm. Collections were made for the degree of anemia.



Fig 5—Absence of rouleaux after saturation of the blood with carbon dioxide. Sickling is about 100 per cent.

**Comment**—Since it is well known that the rate of sedimentation is directly proportioned to the degree of rouleau formation, these results are not surprising. The extent to which carbon dioxide and oxygen influenced these phenomena,

8 Cutler, J. W., Park, F. R., and Herr, B. S. The Influence of Anemia on Blood Sedimentation, *Am J M Sc* 195 734-751, 1938.



however, is interesting. In active sickle cell anemia the rouleaux are imperfect. They can be made normal by saturation with oxygen and made to disappear completely with carbon dioxide. The mechanism of the action of these gases is unknown, whether it is the carbon

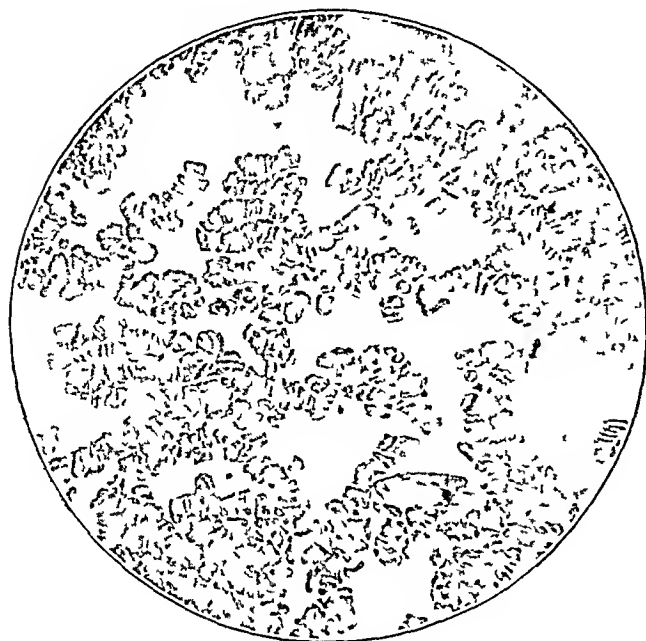


Fig 6—"Normal" rouleau formation after saturation of the blood with oxygen

dioxide or the lack of oxygen that is important has not been definitely determined. The studies with a negative pressure tend to indicate that it is the presence of carbon dioxide that is important. This will be discussed further. These gases might ultimately produce their effects by changing the structure of the erythrocytes, for it has been shown that sickling is increased by carbon dioxide and decreased by oxygen. It would seem to be difficult to stack sickled cells neatly in rouleaux. Of course, there are many other conceivable possibilities that could explain these findings. In many instances, blood saturated or partly saturated with carbon dioxide showed an "abnormal" type of rouleaux when viewed immediately on removal from the flask. The sedimentation rates of these bloods were slow, although free sickle cells were not yet in abundance. When free sickle cells were in abundance the sedimentation rate was invariably slow. This suggests that there are other factors beside the type of rouleaux which affect the sedimentation rate after gaseous saturation, although the type of rouleaux seems to be of great importance.

As will be shown in the next group of experiments, the sickling, rouleau formation and slow sedimentation rate are reversible. Fluctuations from one state to the other can be made to take place with the use of oxygen and carbon dioxide.

#### REVERSIBILITY OF THE SEDIMENTATION RATE

The reversibility of the sedimentation rate was studied in 5 patients with sickle cell anemia and 3 patients with disease states other than sickle cell anemia. A sample of blood of each of the patients was collected and saturated with carbon dioxide and then with oxygen or with oxygen and then with carbon dioxide. The saturations were carried out in Erlenmeyer flasks as previously described. The sedimentation rate was determined after the blood was saturated with each gas.

**Results**—The results are graphically summarized in part by figure 8. As found in the group of experiments immediately preceding, carbon dioxide greatly retarded sedimentation of the erythrocytes of blood showing sickle cell anemia and oxygen accelerated it.

When the sedimentation rate was retarded by carbon dioxide, saturation of the blood with oxygen would accelerate the rate of sedimentation, increasing it to what it was when only oxygen was used, making it even more rapid than that for venous blood alone. Carbon dioxide would retard sedimentation of erythrocytes of blood previously accelerated with oxygen. The marked quantitative changes produced by these gases may be noted in figure 8. No attempt was made to learn the number of times the rate could be reversed by serially alternating the saturations of the blood with oxygen and carbon dioxide, although the

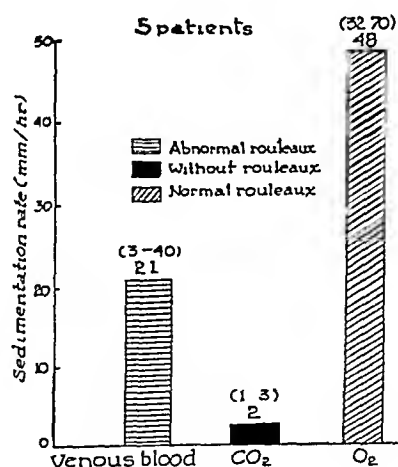


Fig 7—The relation between the type of rouleau formed and the sedimentation rate

sedimentation rate was reversed in 2 patients when oxygen, carbon dioxide, oxygen, and carbon dioxide were used consecutively.

The sedimentation rates of the erythrocytes of the control group of subjects were also changed, but these changes varied qualitatively as well as quantitatively, the changes never being

as dramatic as with sickle cell anemia and, in some cases, not even being reversible (fig 8A)

*Comment*—These findings are in keeping with those found in the preceding study and similarly show a correlation with rouleaux and sickling. The fact that the sedimentation rate

with studies of Smirk,<sup>9</sup> who found increases of cell volume as great as 17 per cent after saturation of blood with carbon dioxide

It was noted in freshly drawn venous blood that the degree of sickling was less among the cells taken from the upper part of the erythrocyte layer in the Wintrobe tube and greater among cells taken from the bottom. It is possible that there is greater anoxia among the latter group of cells. Theoretically, therefore, the cells at the bottom would tend to fall more slowly and impede the fall of the more rapidly settling and better oxygenated erythrocytes near the top of the erythrocyte column.

#### Reversibility

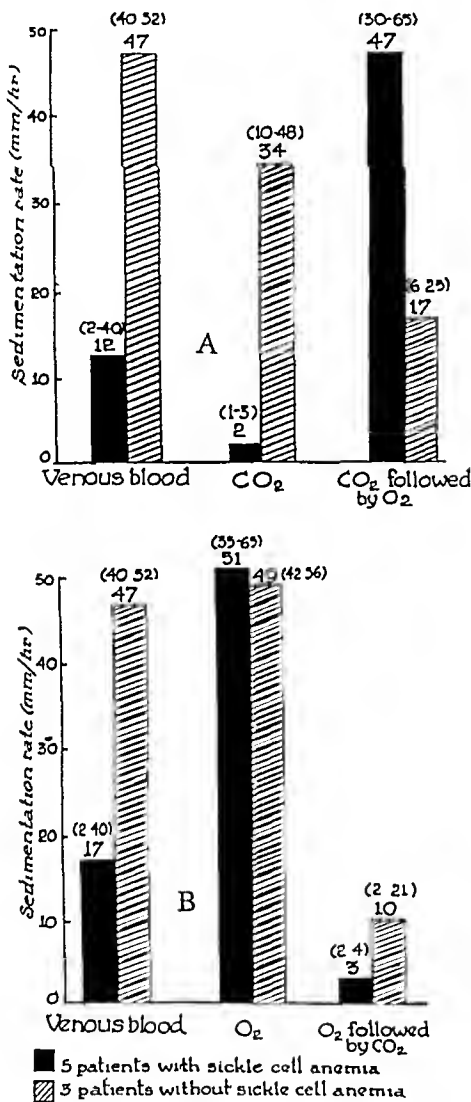


Fig 8—The effect of the successive saturation of a single sample of blood of patients with and without sickle cell anemia (A) with oxygen and then with carbon dioxide and (B) with carbon dioxide and then with oxygen

of the blood of the patients with sickle cell anemia was reversible and that of the controls was not reversible (fig 8A) suggests an interesting qualitative difference between blood of persons with sickle cell anemia and with other types of disease. This qualitative difference was not noted when oxygen was administered first (fig 8B). It is necessary that a much larger number of bloods from patients with many types of disease states be studied before the significance of these findings can be evaluated.

Saturation of the blood with carbon dioxide increased its packed cell volume, the increase being as great as 12 per cent. This is in keeping

#### EXPOSURE OF BLOOD TO AIR AND THE SEDIMENTATION RATE

The effect of blood's standing in air on the sedimentation rate was studied in 3 patients with sickle cell anemia and 3 patients with other clinical states. Five cubic centimeters of blood from each patient was allowed to stand in a 50 cc Erlenmeyer flask for sixty minutes. The flask was rotated for one minute out of every fifteen. Sedimentation rates were determined before and after exposure to air.

*Results*—The sedimentation rate of the blood of patients with sickle cell anemia was increased to approximately three and one-half times the sedimentation rate determined immediately after the blood was drawn from the vein. The sedimentation rate of the control bloods was unchanged (figs 9A and 10).

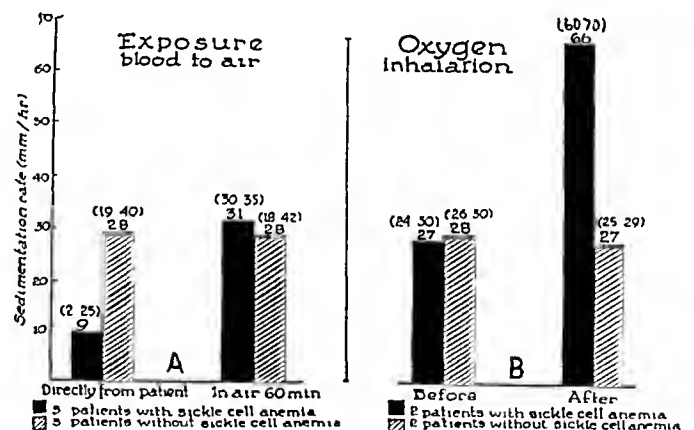


Fig 9—A, the sedimentation rate before and after exposure of blood to air for sixty minutes. B, the sedimentation rate before and after inhalation of 100 per cent oxygen for twenty-three minutes.

*Comment*—The acceleration of the sedimentation rate of blood exposed to air in patients with sickle cell anemia is similar to that seen when the blood of such patients is saturated with oxygen. In the experiments in which blood was saturated

9 Smirk, H. F. The Accurate Measurement of the Proportion of Corpuscles and Serum in Blood, *Brit J Exper Path* 9:81-89, 1928.

with 100 per cent oxygen the sedimentation rate was twice the sedimentation rate of blood taken directly from patients. The increase in the settling rate of blood standing in air (about 20 per cent oxygen) was of the same order of magnitude as that seen when 100 per cent oxygen was used.

The state of previous gaseous saturation of the blood is probably important in determining the degree of acceleration of the sedimentation rate when blood stands in air. Cardiac disease, pulmonary disease or muscular exertion contributes to anoxia and an accumulation of carbon dioxide. If blood from such patients is allowed to stand in air and become oxygenated, a greater acceleration of sedimentation rate may result than if the blood were not initially anoxic. This situation may be comparable to the *in vitro* acceleration by oxygen of the sedimentation rate of blood

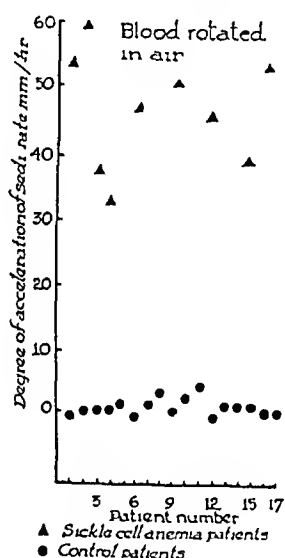


Fig 10—The degree of change produced by aeration of venous blood in the sedimentation rates of the erythrocytes of patients with sickle cell anemia and with other clinical states

previously saturated with carbon dioxide. The sedimentation rate was accelerated twenty-three times by such a procedure (fig 8A).

#### OXYGEN INHALATION AND THE SEDIMENTATION RATE

In the previous studies the effects of oxygen were observed *in vitro*. In order to observe its effects *in vivo* on the sedimentation rate, 2 subjects with sickle cell anemia and 2 subjects with an anemia other than the sickle cell type were made to breathe 100 per cent oxygen for twenty-three minutes in a clinical Benedict-Roth basal metabolism apparatus. The exhaled carbon dioxide was removed with soda lime. The sedimentation rate of the erythrocytes of each subject was measured before and after the breathing of oxygen.

**Results**—The results are summarized in figure 9B. The sedimentation rates of the erythrocytes of the patients with sickle cell anemia were accelerated *in vivo*, as well as *in vitro*, while the sedimentation rates of the other subjects were not affected. The sedimentation rates of the subjects with sickle cell anemia were more than doubled by the inhalation of oxygen.

**Comment**—The fact that the sedimentation rates of the patients with sickle cell anemia were so greatly accelerated by their breathing 100 per cent oxygen indicates that the blood of these patients is not fully saturated with oxygen when they are breathing air. It also shows the need for controlling oxygen saturation of the blood of these patients when studying their erythrocytes.

The effect of oxygen on several phases of the blood other than the sedimentation rate for patients with sickle cell anemia has been studied by others.<sup>10</sup>

#### THE TOURNIQUET AND THE SEDIMENTATION RATE

The sedimentation rate was determined for 4 patients with sickle cell anemia and 4 patients with other disease states before and after the application of a tourniquet. A blood pressure cuff, used as the tourniquet, was placed around the arm of each subject, and the pressure in the cuff was increased to a level just above the diastolic blood pressure. Blood was collected from the antecubital vein below the tourniquet at the end of sixty seconds and again at the end of ten minutes.

**Results**—The results are shown in figures 11A and 12. The sedimentation rates of the subjects with sickle cell anemia were markedly decreased, while those of the other subjects were not changed. The sedimentation rate of 1 of the patients with sickle cell anemia was only 5 mm in one hour initially and was reduced to 2 mm by the tourniquet. Application of the tourniquet produced an increase in the packed cell volume of both groups of subjects.

10 (a) Reinhard, E. H., Moore, C. V., Dubach, R., and Wade, L. J. The Effect of Breathing 80% to 100% Oxygen on the Erythrocyte Equilibrium in Patients with Sickle Cell Anemia, *Proc. Central Soc. Clin. Research* **15**: 13-14, 1942. (b) Hahn, E. V., and Gillespie, E. B. Sickle Cell Anemia, *Arch. Int. Med.* **39**: 233-254 (Feb.) 1927. (c) Schriver, J. B., and Waugh, T. R. Studies on a Case of Sickle Cell Anemia, *Am. J. M. Sc.* **181**: 134, 1931, abstracted, *Canad. M. A. J.* **13**: 375, 1930. (d) Klinefelter, H. F. The Heart in Sickle Cell Anemia, *Am. J. M. Sc.* **203**: 34-51, 1942. (e) Sherman, I. J. The Sickling Phenomenon with Special Reference to the Differentiation of Sickle Cell Anemia from the Sickle Cell Trait, *Bull. Johns Hopkins Hosp.* **67**: 309-324, 1940.

*Comment*—The results of this group of experiments were to be expected in view of the previous *in vitro* studies of the effects of saturation of the blood with carbon dioxide. A venous stasis as produced by the tourniquet results in a decrease of the oxygen content and an increase of the carbon dioxide content of the venous blood. One subject with sickle cell anemia had an initial sedimentation rate of 5 mm in one hour and this rate was decreased to 2 mm by venous stasis, a decrease of 3 mm, or a change of 60 per cent. The initial rate was so slow that one would not expect as great a reduction as in a subject whose initial rate was much more rapid, e. g. 30 mm or more in an hour.

Furthermore, these results show the extreme importance of controlling the length of time the tourniquet is applied when one is collecting blood for study in patients with sickle cell anemia. A great part of the change produced by the tourniquet must be due to the gaseous changes that result, but hemoconcentration, with

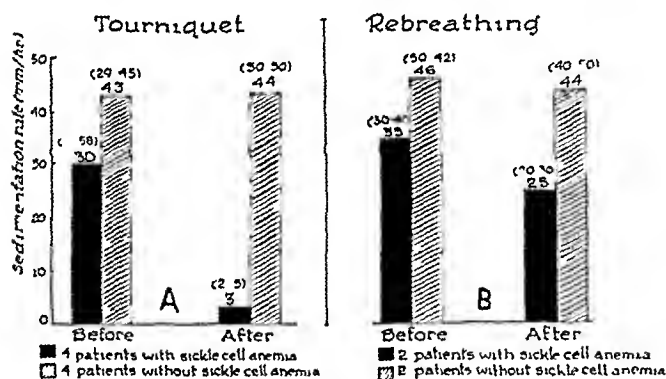


Fig 11—*A*, the sedimentation rate before and after the application of a tourniquet for ten minutes. *B*, the sedimentation rate before and after rebreathing into a bag.

an increase in the plasma protein, concentration of the cellular elements and the like, probably plays an important role.

#### EFFECTS OF REBREATHING ON THE SEDIMENTATION RATE

This group of experiments, like the preceding two, were *in vivo* studies. The sedimentation rates of 2 patients with sickle cell anemia and 2 with other disease states were determined before and after each rebreathed into a bag. They were allowed to breathe into the bag for two minutes, or until they showed symptoms of carbon dioxide accumulation.

*Results*—The sedimentation rates of the 2 patients with sickle cell anemia were slowed 40 per cent, whereas there was no significant slowing of the rates of the other 2 patients (fig 11 *B*).

*Comment*—The effect of rebreathing is similar to that produced by application of a tourni-

quet or by saturation of the blood *in vitro* with carbon dioxide. These results indicate the importance of controlling the systemic accumulation of carbon dioxide generally when studying the blood of patients with sickle cell anemia.

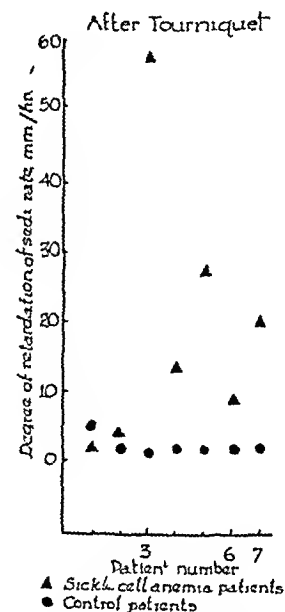


Fig 12—The degree of retardation by the application of a tourniquet of the sedimentation rates of the erythrocytes of patients with sickle cell anemia and with other clinical states.

#### CORRELATION OF INFLUENCE OF OXYGEN, AIR AND CARBON DIOXIDE AND OF THE TOURNIQUET ON THE SEDIMENTATION RATE

Figure 13 illustrates, on the one hand, the similarity of the effects of saturation of blood with oxygen and with air in accelerating the sedimentation rate of the erythrocytes of persons

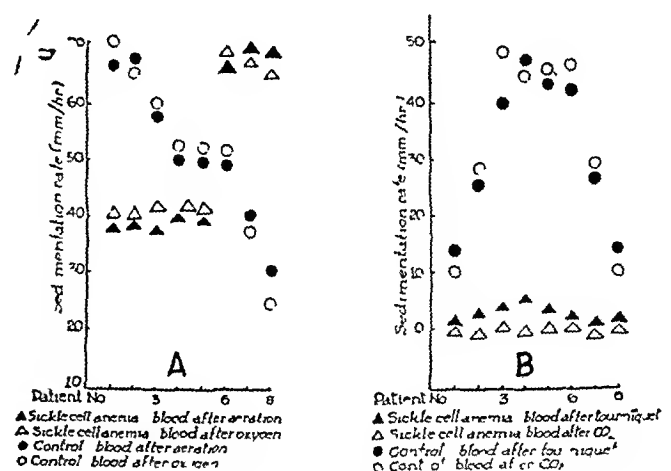


Fig 13—*A*, the close relation between the degree of acceleration of the sedimentation rate produced by aeration and by oxygenation of venous blood from patients with sickle cell anemia and with other clinical states. *B*, the close relation between the degree of retardation of the sedimentation rate produced by application of a tourniquet and by saturation of venous blood with carbon dioxide.

with sickle cell anemia and, on the other hand, the similarity of saturation of blood with carbon

dioxide by means of the pure gas and by venous stasis (tourniquet) These figures also show the lack of such changes in the bloods of patients with clinical states other than sickle cell anemia

CORRELATION OF THE  $p_H$  OF WHOLE BLOOD AND THE SEDIMENTATION RATE

Table 3 shows the relation of the  $p_H$  of whole blood to the sedimentation rate of the blood of 4 patients with sickle cell anemia and 4 patients with other clinical states Two of the latter had anemia Separate samples of blood from each patient were saturated with oxygen, air and carbon dioxide, and the  $p_H$  was determined potentiometrically with a  $p_H$  meter accurate to 0.01  $p_H$  The double oxylate solution already described was used as the anticoagulant, except for the blood of patients 7 and 8 of table 3 Ten

ALTERATION OF THE  $p_H$  BY MEANS OF OXALIC ACID AND ITS EFFECT ON THE SEDIMENTATION RATE

Five cubic centimeters of blood from patients 5 and 6 (table 3) were saturated with air Crystals of oxalic acid were added until the  $p_H$  approached that found when the bloods were saturated with carbon dioxide Sedimentation rates were then determined The results are shown in table 4

The sedimentation rates were altered only slightly by this procedure Patient 5 had a sedimentation rate of 38 mm per hour in air when the  $p_H$  was 7.69, and after acidification with oxalic acid to a  $p_H$  of 6.02 the sedimentation rate became 45 mm per hour Patient 6 had a sedimentation rate of 41 mm per hour after aeration ( $p_H$  7.68) After acidification to a  $p_H$  of 6.32

TABLE 3—Relation Between the Sedimentation Rate, the  $p_H$  of Whole Blood and Saturation of the Blood with  $O_2$ , Air and  $CO_2$  for Four Patients with Sickle Cell Anemia and Four Patients with Other Conditions

Patient No	Diagnosis	Oxygen		Air		Carbon Dioxide	
		Sedimentation Rate, Mm per Hr	$p_H$	Sedimentation Rate, Mm per Hr	$p_H$	Sedimentation Rate, Mm per Hr	$p_H$
1	Ulcerative colitis	24	7.62	22	7.62	19	6.40
2	Gout	47	7.66	46	7.61	42	6.45
3	Bleeding peptic ulcer	21	7.63	20	7.61	19	6.47
4	Bleeding peptic ulcer	52	7.78	50	7.63	50	6.43
6	Sickle cell anemia	40	7.71	39	7.69	1	6.42
5	Sickle cell anemia	45	7.64	41	7.63	1	6.32
7	Sickle cell anemia	57	8.25	63	8.10	1	6.69
8	Sickle cell anemia	43	8.28	50	8.12	1	6.78

\* The  $p_H$  values were the values found for the whole blood after saturation with the respective gases

milligrams of potassium oxylate for each 6 cc of blood was used for these 2 patients

The blood saturated with oxygen or air was alkaline, and the blood saturated with carbon dioxide was acid The sedimentation rates of the erythrocytes both of the control subjects and of patients with sickle cell anemia were slower when the blood was acid than when it was alkaline For the latter group the sedimentation rates in acid and in alkaline mediums were markedly different, the range of difference being from 39 to 56 mm per hour For the control group the difference varied from 2 to 5 mm per hour The  $p_H$  values for the patients with sickle cell anemia and the control subjects were not significantly different

Comment—The changes in  $p_H$  brought on by the saturation of the blood samples with oxygen or carbon dioxide were expected The next experiment was conducted in order to learn whether or not the changes in sedimentation were related to the  $p_H$  of the blood

with oxalic acid, the sedimentation rate was 36 mm per hour

Comment—From these experiments it would seem that it is not the changes in  $p_H$  produced

TABLE 4—The Relationship Between the Sedimentation Rate of the Erythrocytes and the  $p_H$  of Whole Blood of Two Subjects with Sickle Cell Anemia\*

Patient No	Aeration		Acidification with Oxalic Acid	
	Sedimentation Rate	$p_H$	Sedimentation Rate	$p_H$
5 (table 3)	39	7.69	45	6.02
6 (table 3)	41	7.68	36	6.32

\* The bloods were first aerated and then the  $p_H$  and sedimentation rates measured The oxalic acid crystals were then added very slowly in order to reduce the  $p_H$  to about the level produced by saturation with carbon dioxide (table 3) and then the sedimentation rate was measured again

by carbon dioxide or oxygen that are responsible for the effects on sedimentation produced by these gases These gases must produce their influence through some other mechanism than the mediation of  $p_H$

## GENERAL COMMENT

The experiments described illustrate some of the factors which may alter the sedimentation rate of the blood of patients with sickle cell anemia. Inhalation of oxygen, exposure of blood to air and oxygenation of blood *in vitro* accelerate the sedimentation rate. Rebreathing into a bag, application of a tourniquet and saturation of blood with carbon dioxide *in vitro* all retard the sedimentation rate. These changes occur independently of the  $p_H$  and at least depend on the degree of carbon dioxide saturation of the blood.

Oxygen restores sickled cells to the discoid form, fosters normal rouleau formation and restores the sedimentation rate to about the expected rate for the degree of anemia. This supports the value of oxygen therapy in the acute crisis of sickle cell anemia. However, Reinhard<sup>10a</sup> administered 100 per cent oxygen by means of an oxygen mask continuously for from eight to twenty days and noted a fall in the reticulocyte and the erythrocyte count. He interpreted this to indicate a depression of erythropoiesis. There is a need for further studies of this nature. In spite of these findings, it may be advisable to administer a proper concentration of oxygen to patients with severe active sickle cell anemia in the hope that the oxygen will restore the circulating erythrocytes to a more normal state.

When operation is necessary for these patients, an anesthetic gas which does not produce anoxemia is probably preferable. Correct choice of the anesthetist is as important as the choice of the anesthetic agent. Avoidance of anoxemia by proper technic may favor a successful outcome of a surgical procedure. The effect of anesthetic gases on the blood of patients with sickle cell anemia has not been studied, to our knowledge. It would seem, however, that gases requiring a minimum of oxygen to produce satisfactory anesthesia, such as nitrous oxide, would be contraindicated, whereas gases which allow full oxygenation of the blood during anesthesia, such as ether, would be preferable.

A changing sedimentation rate in the same patient from day to day has been mentioned.<sup>2</sup> This may be due to changes in the disease state of the patient or in other physiologic states which vary normally, such as the oxygen and the carbon dioxide content of the blood. It has been shown that these gases may influence greatly the sedimentation rate. It is also likely that the inconstancy of results reported by others is due to variations of technic employed in the collec-

tion of the blood or in the handling of the blood once it was collected. It has been shown in these studies that the duration of application of a tourniquet has a marked effect on the sedimentation rate. This is also true of the length of time the blood is exposed to air. It is likewise possible that the sedimentation rate is slower for venous blood than for arterial blood.

Equal degrees of change in  $p_H$  produced either by carbon dioxide saturation of whole blood or by addition of oxalic acid to the blood did not result in similar effects on the sedimentation rates of the erythrocytes of persons with sickle cell anemia. Carbon dioxide delayed sedimentation, while oxalic acid had no effect. In the control groups, an equal  $p_H$  change produced either by carbon dioxide or by oxalic acid had no significant effect on the sedimentation rate of the erythrocytes. These findings suggest that carbon dioxide *per se* and not necessarily the change in  $p_H$  produced by the carbon dioxide is the significant factor that so markedly influences sedimentation.

It is not difficult to understand how simple it is to find variable results in the sedimentation rate of the blood of persons with sickle cell anemia when so many factors produce such great changes. These observations indicate the need for controlling rigidly the method employed when comparing data for a single patient or for different patients. In view of the many factors affecting the sedimentation rate, it is difficult to interpret the sedimentation rates recorded in the literature, especially when the methods used were not carefully controlled or described in detail. In order to standardize more the methods used in studying the blood of patients with sickle cell anemia, the following suggestions are made.

- 1 The patient should be examined for evidence of pulmonary or cardiac disease or any other state which tends to produce anoxia, so that the degree of anoxemia can be estimated.

- 2 He should rest for fifteen minutes before blood is drawn, so that his blood will reach a state of chemical equilibrium.

- 3 A tourniquet should be allowed to remain on the arm for not longer than sixty seconds during the withdrawal of the blood, and the technic should be constant when patients are compared.

- 4 A quantity of blood should be drawn which will almost fill the vial into which it is to be placed, since this prevents excessive oxygenation of the blood. The vial should be corked immediately and rotated only sufficiently to insure mixing of the blood and the anticoagulant.



5 A dry anticoagulant should be used, so as not to introduce gases contained in a fluid anticoagulant

6 The sedimentation rate should be determined immediately, at a fairly constant temperature

It is well to point out again that the degree of change in the sedimentation rate produced by factors which influence sedimentation, such as oxygen, carbon dioxide and air, depends to a great extent on the initial rate of sedimentation. All factors being equal, oxygen will produce a greater acceleration of sedimentation if the initial value is low and carbon dioxide will produce a greater deceleration if the initial rate is rapid, and vice versa. For such reasons, it is difficult to compare or to evaluate the amount of change, and it is therefore better to compare levels reached when the sedimentation rate is changed. The application of these principles to the diagnosis of sickle cell anemia will be considered in a subsequent report.

#### SUMMARY

Several groups of experiments demonstrate some of the factors which influence the sedimentation rate of the erythrocytes of patients with sickle cell anemia.

The sedimentation rates of 6 of 10 patients with sickle cell anemia were slow when compared with their packed cell volumes. The patients with the most severe anemia had the slowest sedimentation rates.

Additional anemia produced artificially in the blood of patients who already had mild or severe anemia did not produce a comparable slowing of the sedimentation rate. It is therefore not the anemia itself which produces the slow sedimentation rate, but some other factor which changes concomitantly with the decrease in erythrocytes.

The data indicate strongly that it is carbon dioxide *per se* and not the change in  $p_H$  produced by carbon dioxide that so significantly slows the rate of sedimentation of the erythrocytes.

The sedimentation can usually be correlated with the type of rouleau formation, being rapid when rouleaux are "normal," somewhat slow when they are "abnormal" and very slow when they are absent. Although the sedimentation rate was invariably slow when rouleau formation was absent, the slow rates seen when rouleaux were abnormal suggests that other factors besides the formation of rouleaux affect the sedimentation rate.

The sedimentation rate of blood saturated with oxygen was invariably accelerated, and the sedimentation rate of blood saturated with carbon dioxide was invariably retarded. The retardation was frequently so great that severely anemic blood did not settle more than 2 or 3 mm in four or five days.

The sedimentation rate is accelerated by placing blood in a vacuum of 780 mm of mercury for twenty-three minutes. Carbon dioxide probably greatly retards the sedimentation rate by mechanisms other than mere exclusion of oxygen.

The sedimentation rates of patients with sickle cell anemia could be slowed or accelerated by alternate saturation with carbon dioxide and oxygen, that is, the sedimentation rates were reversible and varied considerably. Normal blood was affected only slightly by these gases.

Inhalation of pure oxygen accelerated the sedimentation rate, as did also exposure of the blood to air.

Keeping a tourniquet on the arm for ten minutes retarded the sedimentation rate, as did also rebreathing into a paper bag.

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# Progress in Internal Medicine

## GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM  
JULY 1942 TO JULY 1943

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A review of the literature regarding physiology and disease of the digestive tract is of particular interest at the present time. Gastrointestinal disease and disturbances of gastrointestinal function constitute one of the most important medical problems of the war, affecting both the armed forces and civilians. Because of this fact, the present review will include mention of many articles that do not contain strictly new material but which may call attention to the numerous factors influencing the behavior of the alimentary tract.

### PHYSIOLOGIC ASPECTS

Perusal of the literature on this subject reveals more than ever the multiplicity of factors entering into properly integrated gastrointestinal function. Many of these factors are still little understood or purely hypothetical, but on the whole a much clearer understanding is apparent of the relationship between the nervous system, the glands of internal secretion and gastrointestinal function.

*Motor Aspects*—An excellent general discussion of digestion and the nervous system is that of Thomas,<sup>1</sup> who outlines first the extrinsic innervation of the stomach and of the small and the large bowel. He discusses the effects of vagotomy and sympathectomy on the motor activity of the various levels of the digestive tract. Thus the immediate effect of vagotomy is pronounced loss of tonus and motility in the fasting stomach, whereas section of the splanchnic nerves has less effect on gastric motility than division of the vagi. In the small bowel parasympathetic denervation has apparently only minor effects on the activity of the smooth muscle, but stimulation of the sympathetic nerves, as a rule, results in loss of tone and cessation of motility. Stimulation of the parasympathetic innervation of the large intestine via the pelvic nerves appears to augment the activity of both the circular and the longitudinal muscles of the large intestine and at the same time to cause relaxation of the internal anal sphincter. Removal of the inferior mesenteric ganglion in dogs causes a persistent diarrhea. The predominant action of the sympathetic innervation of the large bowel appears to be largely inhibitory. Thomas also discusses the innervation of the digestive glands and central mechanisms. He refers particularly to the recent studies by Wolf and Wolff in relation to the effects of emotional disturbances. As an informative and enlightening presentation of the factors influencing gastric function, the reviewer would like to give particular credit to the experimental studies of these two investigators.<sup>2</sup> Their most important

1 Thomas, J. E. Digestion and the Nervous System. A Review of the Literature, *Am J Digest Dis* **10** 201, 1943.

2 Wolf, S., and Wolff, H. G. Human Gastric Function, New York, Oxford University Press, 1943. Richards, C. H., Wolf, S., and Wolff, H. G. The Measurement and Recording of Gastroduodenal Blood Flow in Man by Means of a Thermal Gradientometer, *J Clin Investigation* **21** 551, 1942. Wolf, S., and Wolff, H. G. The Gastric Mucosa, "Gastritis" and Ulcer, *Am J Digest Dis* **10** 23, 1943.



results and a summary of their work appear in a recent publication, which warrants careful study by any one interested in the fundamentals of gastric physiology and disease. In this volume is to be found a most excellent description of the changes occurring in the gastric mucosa involving motor activity and secretion and blood flow under varying conditions. The effect of various emotional states on gastric emptying time, the vascularity of the stomach and sensation in the stomach and the mechanisms underlying gastric symptoms are discussed in detail and bring up to date in an easily visualized manner the original observations of Beaumont on Alexis St. Martin. The measurements of blood flow in the stomach, for example, are of extreme interest. Contractions of the wall of the stomach and duodenum were accompanied by transitory acceleration of blood flow. Histamine induced a prolonged acceleration of blood flow in the gastric mucosa. The mere discussion of appetizing food was accompanied by an accelerated blood flow, and emotional states resulting in anxiety, resentment and tension had a similar effect. The general discussion by Thomas and the very careful investigations of Wolf and Wolff, which are presented in book form, together give an excellent background for any consideration of gastrointestinal physiology, particularly in relation to gastritis and gastric ulcer.

In any discussion of the "normal" responses in a given system, it is important to stress the wide variations that may be encountered. Van Liere and Northup<sup>3</sup> have studied the emptying time of the normal human stomach in the young adult in order to establish a criterion of the normal gastric emptying time. Sixty-nine subjects were observed under standard conditions and by repeated tests. Fluoroscopic studies showed that the average emptying of a standard meal of cereal and barium sulfate occurred at two and one-tenth hours, extremes ranged from one and five-tenths to three and three-tenths hours. These figures, of course, apply only to a given technic with a given motor meal, but they at least offer a basis for comparative studies on gastric motor activity in human beings and supplement the studies made by these authors on other age groups.

The effect of hydrochloric acid on the pyloric sphincter was studied by Quigley and his associates.<sup>4</sup> Their studies were carried out on dogs by the use of experimental balloons, and evidence was obtained that hydrochloric acid in the stomach exerts little or no physiologic action on the motor activities and pressure changes in the pyloric sphincter region or on the process of gastric evacuation. In the duodenum, hydrochloric acid is moderately effective in suppressing the pyloric antrum and thus retards gastric evacuation, presumably to bring about a more complete neutralization of acid values in the duodenum.

Winfield and Kaulbersz<sup>5</sup> found that solutions of dried bile or bile salts induced gastric hunger contractions when placed in a fasting dog's stomach, an action which was inhibited by subcutaneously injected atropine sulfate. If introduced during the contraction phase, bile, choline, potassium chloride, magnesium salts and calcium chloride cause inhibition of gastric contractions in many instances. Potassium chloride when introduced in the fasting state has an action similar to that of bile. Apparently smooth muscle activity is similar to that of the skeletal muscle with

3 Van Liere, E. J., and Northup, D. W. The Emptying Time of the Normal Human Stomach in the Young Adult, *Gastroenterology* **1** 279, 1943.

4 Quigley, J. P., Read, M. R., Radzow, K. H., Meschan, I., and Werle, J. M. The Effect of Hydrochloric Acid on the Pyloric Sphincter, and Adjacent Portions of the Digestive Tract, and on the Process of Gastric Evacuation, *Am J Physiol* **137** 153, 1942.

5 Winfield, J. M., and Kaulbersz, J. Influence of Bile on Gastric Motility, *J Pharmacol & Exper Therap* **76** 97, 1942.

respect to liberation of potassium Cicardo<sup>6</sup> has observed that electric stimulation of stomach strips or application of acetylcholine in concentrations that produce rhythmic contractions caused a liberation of potassium This effect was increased by physostigmine Atropine prevented the liberation of potassium by acetylcholine Slaughter, Goddard, and Henderson<sup>7</sup> present evidence that the effects of morphine on the stomach can be potentiated by a cholinergic drug Prostigmine methylsulfate was used as the potentiating drug When inactive doses of morphine were given after subliminal doses of prostigmine methylsulfate, a typical morphine-like effect was seen in the stomach, as shown by a rise in tonus and rhythmic activity above the normal level Individual inactive doses of morphine and prostigmine methylsulfate combined in one injection produced a typical morphine-like effect The effects of atropine, prostigmine, epinephrine and calcium on the movements of the fasting human stomach were studied by Anderson and Morris,<sup>8</sup> using a modification of Carlson's balloon method The drugs were administered subcutaneously, intramuscularly and intravenously during different phases of gastric activity In small doses atropine caused an increase in the frequency and amplitude of hunger contractions and a slowing of the pulse, but a second small dose apparently had a sensitizing effect, and thereby an antiparasymphathetic action was obtained In large doses the drug inhibited the movements of the stomach and quickened the heart beat Prostigmine was shown to have an excitator effect on gastric motility, which was not prevented by premedication with atropine unless the latter was given in large doses Epinephrine in small doses occasionally increased gastric motility, but in large doses it consistently had a sedative action, as did calcium The inhibitory action of calcium on the fasting contractions of the stomach was accompanied by a slowing of the heart rate, indicating vagal activity

Further studies on the relation between low oxygen tension and gastric emptying time are to be found in an article by Stickney and Van Liere<sup>9</sup> In this investigation the gastric emptying time after a standard meal was determined for 5 dogs during discontinuous exposure to reduced oxygen tension simulating altitudes of 12,000, 16,000 and 18,000 feet The usual delay in gastric emptying produced by anoxia was found to be gradually reduced in every case The return to normal gastric emptying under these conditions was complete at tensions of 100 mm of oxygen and 86 mm of oxygen At 80 mm of oxygen tension (18,000 feet, equivalent), only 1 dog out of 5 showed a complete return to normal levels Considerable individual variation was found in the time for complete return to normal gastric emptying The persistence of this adaptation of anoxia to the periods of discontinuous exposure was from less than a week to over six months Since gastric emptying time as an index of function may reveal adequacy of the adjustment of the compensatory mechanism during anoxia, the authors suggest that it may be regarded as another criterion of acclimatization In an attempt to find a simple substance which would reduce to normal the increased gastric emptying time produced by anoxia, Stickney<sup>10</sup> investigated the effect of oil of peppermint, dehydrocholic acid and disodium

6 Cicardo, V H Liberation of Potassium During Contractions of Stomach, *Rev Soc argent de biol* **17** 81, 1941

7 Slaughter, D, Goddard, A B, and Henderson, W M Some New Aspects of Morphine Action Effect on the Stomach, *J Pharmacol & Exper Therap* **76** 301, 1942

8 Anderson, W F, and Morris, N The Effects of Atropine, Prostigmine, Adrenaline and Calcium on the Movements of the Fasting Human Stomach, *J Pharmacol & Exper Therap* **77** 258, 1943

9 Stickney, J C, and Van Liere, E J Acclimatization of Low Oxygen Tension in Relation to Gastric Emptying, *Am J Physiol* **137** 160, 1942

10 Stickney, J C Effect of Oil of Peppermint, Dehydrochloric Acid and Disodium Phosphate on Gastric Emptying Time in Dogs, *Proc Soc Exper Biol & Med* **52** 274, 1943

phosphate These agents were chosen because they have been reported to decrease gastric emptying time in human beings and because they have little or no complicating side effects No significant changes were noted after the administration of any of these preparations

In order to evaluate more properly the factor of anoxia in acute gastric dilatation, a comparative study was made by Johnson and Mann<sup>11</sup> on the effects of anesthetics on gastric tonus and motility in the trained dog Studies were made on animals in which the extrinsic gastric nerves were present and on animals that had undergone vagotomy and splanchnicectomy It was found that anesthetics had either a depressing effect on gastric tonus and motility or no effect at all The degree of motor activity was in general directly proportional to the degree of anesthesia produced, regardless of the agent used The authors conclude that this effect is not mediated through the vagus or splanchnic nerves but is due to a primary action on the peripheral gastric motor mechanism The relative quantity of oxygen in the blood and tissues did not appear to be a determining factor Striking individual susceptibility was noted, as might have been expected Premedication with morphine and atropine definitely prolonged the depressing effect of ether, an important point in relation to preoperative medication The depth of the anoxia appeared to be more important than its duration

Necheles and his collaborators<sup>12</sup> made determinations of gastric motility in dogs following the injection of various pyrogens Pentnucleotide, thymus and yeast nucleic acid, *Bacillus coli* vaccine, triple typhoid vaccine and a crystalline preparation of a bacterial pyrogen were used In a great number of experiments depression of the gastric motility resulted, with no change in rectal temperature and with no subjective signs in most of the animals This depression of motor activity was prolonged The relation of this finding to "dyspepsia" during infections of the upper respiratory tract and other infectious diseases in which no or only a slight elevation of body temperature occurs is discussed The authors feel that the threshold of the temperature center is higher than that concerned with gastric motility They also suggest that preparations of depressants of gastric motility and secretion, such as pepsin and enterogastrone, may be contaminated with small amounts of pyrogenic substances

The close relationship between changes in gastric and duodenal tonus and the resistance of the sphincter of Oddi were studied by Leskovar<sup>13</sup> Manometric readings of alterations in the secretory pressure in the bile duct were recorded in rabbits and dogs at the same time that intragastric pressures were recorded Heat applied to the skin produced an increase in gastric pressure and a similar increase in the resistance of the sphincter of Oddi Emesis in dogs caused an especially marked decrease of sphincter tonus, and the subcutaneous injection of atropine also decreased the tonus of the duct sphincter, but pilocarpine increased it A parallel relationship was seen to exist between changes in gastric and duodenal pressure and changes in tonus of the sphincter of Oddi Apparently the determining factor influencing the functional activity of the distal portion of the bile duct was the internal pressure in the stomach and duodenum

11 Johnson, C R, and Mann, F C The Effect of Anesthetics on Gastric Tonus and Motility with Special Reference to Acute Gastric Dilatation, *Surgery* **12** 599, 1942

12 Necheles, H, Dommers, P, Wiener, M, Olson, W H, and Rychel, W Determination of Gastric Motility Without Elevation of Body Temperature Following Injections of Pyrogens, *Am J Physiol* **137** 22, 1942 Necheles, H Depression of the Stomach by Non-specific Substances, *Proc Inst Med Chicago* **14** 345, 1943

13 Leskovar, R Function of the Sphincter of Oddi, *Arch f exper Path u Pharmakol* **197** 361, 1941

Some confirmation of Alvarez' conception of an intestinal gradient is to be found in an article by Chang and Hsu<sup>14</sup> on the chemical excitability of the isolated small intestine of the rabbit. Under standard conditions, segments were taken from different levels of the intestinal tract and were simultaneously studied as to their relative excitability. Segments from the upper levels of the intestine were generally more sensitive to acetylcholine, while those from the lower levels were more sensitive to epinephrine. This gradient of chemical excitability was easily upset by shock and asphyxia of the animal. The stimulating action of barium, physostigmine, histamine, pilocarpine and choline and the depressing action of atropine, potassium and magnesium appeared to be about equal in all the segments. The difference in excitability of the intestinal musculature to the neurohormone was regarded as an innate property of the muscle fibers at the different levels.

The effect of intravenously administered dextrose on the motor activity of the stomach and intestine was studied by Belenkov<sup>15</sup> and is of interest in relation to its possible effects following routine intravenous therapy. In fasting dogs, a 20 cc dose of a 10 per cent solution of dextrose lowered the motor activity of the intestine and reduced the amplitude of and increased the intervals between the contractions, and a similar dose of a 20 per cent solution further inhibited intestinal contractions and increased the interval of contractions to twenty minutes. This dose also affected gastric activity, shortening the periods of hunger contractions and lengthening the intervals. While gastric hunger contractions continued, intestinal activity was not affected by dextrose. Twenty cubic centimeters of a 30 per cent solution of dextrose had an even greater effect on gastric and intestinal activity. In the intervals between intestinal contractions there were periods of complete rest. These responses were observed in an animal with an intact sympathetic nervous system. For an animal with a denervated intestinal tract, a dose of 40 cc of a 40 per cent solution of dextrose was required before a distinct depression of the intestinal contractions could be noted. The application of such observations to the routine care of patients postoperatively would seem to indicate that the depressing effect of anesthesia and preoperative medication would be augmented and prolonged by the use of very hypertonic solutions of dextrose and that, as a rule, such solutions should be avoided.

In vitro confirmation of the effect of concentrated solutions of dextrose is to be found in the studies of Feldberg and Solandt<sup>16</sup>. These authors studied the effect of sugar and allied substances on the isolated small intestine and demonstrated the stimulating effect of optimal amounts of dextrose or certain other sugars on smooth muscle contraction of intestinal segments. In the absence of dextrose, tonic and rhythmic activity gradually ceased, even after stimulation by acetylcholine and other cholinergic drugs. The addition of small amounts of dextrose to the immersion fluid had a stimulating effect on the longitudinal intestinal muscle, but large doses of dextrose, galactose and mannose produced immediate inhibition. In this study differences in the excitability of circular and longitudinal muscle are discussed in relation to general properties of smooth muscle contraction. That the tonicity of solutions affects the motor activity of the intestine is further shown in the studies of Lignon,<sup>17</sup> who studied variations in intraluminal jejunal pressure in dogs follow-

14 Chang, P. Y., and Hsu, F. Y. The Chemical Excitability of the Isolated Rabbit Small Intestine, *Quart. J. Exper. Physiol.* **31** 299, 1942.

15 Belenkov, N. Yu. Effect of Glucose on the Motor Activity of the Stomach and Intestines, *J. Physiol. USSR* **30** 704, 1941.

16 Feldberg, W., and Solandt, O. M. Effects of Sugar and Allied Substances on the Isolated Small Intestine of the Rabbit, *J. Physiol.* **101** 137, 1942.

17 Lignon, E. W., Jr. Cathartic Salts on Motility of Thiry-Vella Jejunal Loops, *Proc. Soc. Exper. Biol. & Med.* **52** 282, 1943.

ing the use of isotonic and hypertonic solutions of sodium chloride, sodium sulfate and magnesium sulfate. Even with these cathartic salts, very hypertonic solutions (5 times isotonicity) caused a temporary depression of motility with short periods of spasticity and nausea. The rate of contraction was unaffected by the agents employed. Hazelton and Fortunato<sup>18</sup> made an evaluation of the cathartic action of bile salts. The threshold cathartic dose of bile salts compound for mice was determined, and one-half this dose was administered to these animals daily for a long period. At various intervals the threshold cathartic dose was given to the treated animals and to a similar number of controls. The results indicate that bile salts produce active catharsis in mice, that there is no tolerance or accumulation and that an appreciable degree of increased susceptibility to the cathartic action of bile salts is produced by their daily administration. This increased susceptibility is specific, as evidenced by the fact that the daily administration of bile salts did not influence the threshold cathartic dose of senna. A somewhat similar method was employed by Loewe and his associates<sup>19</sup> in attempting to evaluate the influence of thiamine on laxative action. The threshold cathartic dose of phenolphthalein was determined in experiments on monkeys, and subsequently thiamine was administered over a varying period in conjunction with this dose. The experiments gave no support to the assumption of a synergistic influence of vitamin B<sub>1</sub> on laxative action.

Differentiation between nonpropulsive and propulsive motility in the ileum and colon forms the basis of further studies by Adler, Atkinson and Ivy<sup>20</sup>. On human subjects with an ileostomy or colostomy observations were made of both types of motor activity. Intramuscular administration of morphine in ordinary clinical doses increased the tone and amplitude of the nonpropulsive type of rhythmic contractions of the segments of the distal portion of the ileum. The propulsive activity of the ileum was uniformly decreased. Dilaudid had a similar effect. Morphine sulfate, in the same doses, usually increased the tone and amplitude of the nonpropulsive type of rhythmic contractions of the segments in the descending colon. In 9 instances in which the colon was manifesting diarrhea the administration of morphine abolished the colostomy discharge by decreasing propulsive motor activity and by reducing tone and segmentation. Atropine produced a decrease in the total motility in the descending colon, with a uniform diminution of propulsive motility. The use of this drug partially antagonized the effect of morphine, providing evidence that the combined use of these drugs in the treatment of severe gastrointestinal pain is logical. Morphine sulfate delays the ileal and colonic passage of material in man primarily by interfering with or diminishing propulsive motility. The authors suggest that morphine causes dyskinesia of the small and large intestine and that motor activity of adjacent segments of the bowel must be coordinated in order that effective propulsion may occur. Further detailed studies on such coordination are to be found in a subsequent paper by Atkinson, Adler and Ivy<sup>21</sup>. Studies were made on human subjects by continuous records during seventy periods of at least one hundred and fifty minutes each. The simultaneous injection of a solution of posterior pituitary, prostigmine methylsulfate and ergotamine tartrate was found to cause a

18 Hazelton, L. W., and Fortunato, F. An Evaluation of the Cathartic Action of Bile Salts Following Acute and Chronic Administration to Mice, *J Am Pharm A (Scient Ed)* **31** 60, 1942.

19 Loewe, S., Loewe, I., and Knox, R., Jr. Thiamine Influence upon Laxative Action *Am J Digest Dis* **10** 65, 1943.

20 Adler, H. F., Atkinson, A. J., and Ivy, A. C. Effect of Morphine and Dilaudid on the Ileum and of Morphine, Dilaudid and Atropine on the Colon of Man, *Arch Int Med* **69** 974 (June) 1942.

21 Atkinson, A. J., Adler, H. F., and Ivy, A. C. Motility of the Human Colon. The Normal Pattern, Dyskinesia and the Effect of Drugs, *J A M A* **121** 646 (Feb 27) 1943.

prompt and prolonged increase in the propulsive motility of the human colon without side reactions. It was shown that morphine sulfate is not an antispasmodic in the sense that all motility is inhibited. As previously indicated, it increases the tone and nonpropulsive motility and definitely decreases or abolishes propulsion. Of the various "antispasmodics" studied, atropine and traserin (a proprietary synthetic ester of diphenylacetic acid and diethylaminoethanol) proved to be the most potent depressants. Intramuscular injections of atropine sulfate may abolish all spontaneous motility of the colon for a brief period, whereas traserin is less likely to do so. The latter may depress nonintegrated motility in such a manner that propulsion is favored and a normal gradient established. In dogs, the effect of these drugs is more striking on the distal than on the proximal portion of the colon. The authors rightly point out that the ideal "spasmolytic" drug for the colon has yet to be discovered. Hallenbeck and his associates<sup>22</sup> have studied the effect of thymoxyethyl-diethylamine (929 F) on gastric and intestinal motility. The intravenous injection of this preparation in dogs caused partial or complete inhibition of spontaneous and postprandial gastric motility in some instances. It usually caused transient inhibition of postprandial and spontaneous motility of duodenal and upper jejunal loops, but appeared to have no effect on the terminal portion of the ileum. Burchell and Varco<sup>23</sup> conclude that this drug and another of the phenoxyethers (N'-ethyl-N'-diethyl-aminoethylamine) have a nonspecific protective action against smooth muscle contraction. They seem to have a strong preferential inhibition on the histamine type of smooth muscle reaction. With large doses of thymoxyethyl-diethylamine administered subcutaneously, some evidence of lowered sensitivity to pain was observed. Complete analgesia was not noted, although this had been claimed by some previous investigators.

According to Canonico and Mann,<sup>24</sup> obstruction of the common bile duct by ligation was followed in animals by a marked decrease of activity in exteriorized loops of jejunum and ileum during the first two weeks after operation. Subsequently intestinal activity increased but never returned to normal in the jaundiced animals. The decrease of motor activity occurred in both fasting and digesting states but was more noticeable in the latter. It is suggested that the retention of biliary constituents in the blood, particularly bile salts, may be the cause of alteration in intestinal activity.

Svien and Mann<sup>25</sup> have studied motor activity of the jejunum and the upper part of the ileum following distention of the gallbladder and the urinary tract. Distention of the gallbladder apparently produced no change in the peristaltic pattern of the jejunum or ileum. Sudden distention of the urinary bladder produced diminution of duodenal activity and inhibited activity in all segments of the upper intestine, the greatest effect being noted in the upper segments. Distention of the upper part of the urinary tract produced inhibition of motility in the jejunum and ileum, which persisted as long as distention was maintained and in some cases for variable periods up to five minutes after the distending pressure had been released. The authors believe that their results are consistent with the hypothesis of a gradient of irritability

<sup>22</sup> Hallenbeck, G. A., Code, C. F., and Mann, F. C. The Effect of Thymoxyethyl-diethylamine (929 F) on Gastric and Intestinal Motility. *An Experimental Study, Gastroenterology* **1** 588, 1943.

<sup>23</sup> Burchell, H. B., and Varco, R. L. The Anti-Histamine Activity of Thymoxyethyl-diethylamine and n'-Ethyl-n'-Diethylaminoethylamine as Judged by the Gastric Response to Histamine, *J. Pharmacol. & Exper. Therap.* **75** 1, 1942.

<sup>24</sup> Canonico, A., and Mann, F. C. Intestinal Activity After Obstruction of Common Bile Duct, *Surgery* **13** 81, 1943.

<sup>25</sup> Svien, H. J., and Mann, F. C. Intestinal Activity Following Distention of the Gall Bladder and Urinary Tract. *An Experimental Study, Surgery* **13** 67, 1943.

from the duodenum caudalward. Since the upper segments of the small intestine are more irritable than are the lower segments, it would seem that the duodenum and the upper portion of the jejunum are less readily inhibited and less readily kept under inhibition by a given stimulus than is the lower part of the ileum. These experiments are of additional clinical interest inasmuch as they tend to reproduce the picture of intestinal obstruction which is occasionally seen in relation to sudden obstruction of some portion of the urinary tract.

A further consideration of the effects of anesthesia on intestinal motility is to be found in an article by Wakim and Mann,<sup>26</sup> who studied the combined results of ether anesthesia and exploratory laparotomy. Such a procedure abolished intestinal activity for at least four hours, but in twenty-four hours the activity of the intestine was practically normal. Section and anastomosis of the intestine abolished intestinal activity for about forty-eight hours, after which rhythmic segmentation and peristalsis reappeared. Feeding inhibited activity in the loop when the site of section and anastomosis was proximal to the loop under observation. After the sixth postoperative day the intestines resumed normal motor activity.

The mechanism of intestinal inhibition by cyclopropane anesthesia was studied by Youmans and his associates,<sup>27</sup> this anesthetic producing great diminution or complete abolition of the rhythmic contractions of the dog's intestine, even when the adrenal glands had been denervated and demedullated. The inhibition was still present under hyperventilation with the cyclopropane-oxygen mixture. The authors conclude that the inhibition of intestinal motor activity by cyclopropane is not dependent on the liberation of epinephrine from the adrenal medulla or on a low oxygen tension in the alveolar air. The relationship between such motor inhibition and postoperative distention is obvious, and the observations of Puestow<sup>28</sup> on a human subject are of interest. In his subject Puestow was able to observe several loops of the jejunum and the upper part of the ileum, as well as the ascending colon, through a large hernial sac. A definite relationship was noted between the motility of the small intestine and that of the ascending colon, the latter being inactive when the small bowel was contracting vigorously, and vice versa. The author was able to confirm the observation that opiates, physostigmine, prostigmine methylsulfate and the choline derivatives, which stimulate motility of the small bowel, inhibit the colon, and that, conversely, solutions of posterior pituitary and pitressin produce powerful contractions of the colon but diminish motor activity of the small bowel. Confirmatory observations were made on 13 other patients with portions of the bowel exposed to direct vision. One important conclusion should be stressed, in the opinion of the reviewer—namely, that postoperative distention may be due in large part to the paralyzing action of morphine on the colon. It is entirely possible that the action of this drug, which is so universally used preoperatively and postoperatively, may be one of the most important factors in the distention and abdominal discomfort subsequent to a major abdominal operation and that its use might be appreciably curtailed with advantage to the patient.

The close relationship between the cerebral cortex and the motor action of the digestive tract is emphasized by the studies of Booligin,<sup>29</sup> who investigated the move-

26 Wakim, K. G., and Mann, F. C. Effects of Some Intra-Abdominal Operative Procedures on Intestinal Activity. An Experimental Study, *Gastroenterology* **1** 513, 1943.

27 Youmans, W. B., Enos, R. W., Karstens, A. I., and Aumann, K. W. The Mechanism of Intestinal Inhibition by Cyclopropane Anesthesia, *Anesthesiology* **3** 303, 1942.

28 Puestow, C. B. Intestinal Motility and Postoperative Distention. Experimental and Clinical Studies, *J. A. M. A.* **120** 903 (Nov. 21) 1942.

29 Booligin, I. A. The Relation Between the Cerebral Cortex and the Motor Action of the Digestive Tract, *Arch. dis. sci. biol.* **54** 65, 1939.



ments of the fundic and pyloric regions of the stomach, of the duodenum, of various portions of the alimentary tract and of the parotid glands. The influence of the cerebral cortex on gastrointestinal motility is accomplished by short cortical impulses caused by sudden "conditioned stimuli" and prolonged cortical impulses caused by prolonged exposure to "food surroundings." The effect of the short impulses appears to depend on the character of the conditioned reflex, that of the more prolonged stimulus, positive or negative, on the section of the alimentary tract involved and on its functional state. "Short" conditioned stimuli caused cortical stimuli initiating gastric and intestinal motility within a few seconds or rarely after one to three minutes and producing an effect lasting from thirty seconds to five minutes. The author believes that by such means the cortex not only regulates motility of the stomach but adapts it rapidly to changing environmental conditions.

Sheehan<sup>30</sup> has elaborated earlier studies on the relationship of the hypothalamus to the large bowel. He obtained results confirmatory of those of others, indicating that adequate hypothalamic stimulation, particularly in the lateral hypothalamic area, is followed by inhibition of peristalsis in the large bowel as well as in the intestine and stomach and that such effects are more marked in the colon than elsewhere. There are adequate grounds, he believes, for accepting the concept of a sympathetic center regulating gastrointestinal activity and located in this area.

Studies on certain aspects of the motor innervation of the colon have received continued attention by Ivy and his collaborators.<sup>31</sup> One series of experiments has been undertaken to supply evidence on certain pertinent questions concerning the chemical mediators of nerve impulses from various nerves to the colon, the region of the colon which responds to stimulation of a given nerve, the pathway by which pelvic nerve impulses influence upper levels of the colon and the similarity between colonic and vesical motor activity following stimulation of the pelvic nerves. In experiments which were carried out on dogs, pigs and monkeys, the authors come to the conclusion that the pelvic nerves to the musculature of the colon are cholinergic. Electrical stimulation of the pelvic nerves causes longitudinal and circular contraction of the descending and the distal portion of the colon. These nerves influence upper levels of the colon via nerve pathways located in the wall of the colon. A dual contractile and tonus mechanism in response to stimulation of the pelvic nerves does not exist in the colon, as has been claimed to exist in the urinary bladder. Electrical stimulation of the vagus nerve is ineffective in producing colonic motility in the dog. Only inconstant cecal contractions were noted in the pig and in the monkey. The hypogastric nerves to the musculature of the colon are adrenergic, and electrical stimulation usually causes a circular contraction which is confined to the distal portion of the colon. The fibers of the celiac root of the inferior mesenteric ganglion which act on the colon are adrenergic, and electrical stimulation of them usually causes a circular contraction which is confined to the descending colon.

Studies on the concentration of acetylcholine in the alimentary tract were made by Bacq and Goffart.<sup>32</sup> The highest concentrations in dogs were found in the upper part of the jejunum, and the lowest concentrations, in the esophagus and in the colon.

30 Sheehan, D. Relationship of the Hypothalamus to the Large Bowel, *Am J Digest Dis* 9 361, 1942.

31 Wells, J. A., Mercer, T. H., Gray, J. S., and Ivy, A. C. The Motor Innervation of the Colon, *Am J Physiol* 138 83, 1942.

32 Bacq, Z. M., and Goffart, M. Free and Combined Acetylcholine in Intestinal Tract, *Schweiz med Wchnschr* 71 310, 1941.



The mucosa always contains less acetylcholine than the muscularis. There appeared to be no parallelism between the tissue concentration of vitamin B<sub>1</sub> and that of acetylcholine.

The conclusion by several investigators that stimulation of the hypothalamic region simultaneously regulates both sympathetic and parasympathetic divisions of the autonomic nervous system finds support in the studies of Mautner and Yetwin<sup>33</sup> and in those of Oppenheimer and his associates.<sup>34</sup> The former noted in rats that injections of metrazol resulted in a cessation of gastric motility with an associated moderate increase in secretory activity. They felt that the effect on gastric motility could not be attributed to an increased output of epinephrine but was probably due to a central effect. Bulbocapnine has been shown to stimulate both the sympathetic and the parasympathetic centers. Oppenheimer and his associates studied the effect of such stimulation in dogs by subcutaneous injection of bulbocapnine phosphate. Sympathetic effects, as regards intestinal motility, were the most important, and the amplitude of contraction was diminished. In vagotomized dogs, loops of intestine just below the duodenum showed an increased amplitude of contraction after medication but in the region of the ileocecal valve inhibition was noted. In splanchnicectomized dogs, the vagus mechanism was activated in respect to the amplitude of intestinal contractions, except for the effect on the blood sugar levels, which were raised. The drug did not change the rate of intestinal contractions. The effect of vagotomy and of sympathectomy on the sensitivity of intestinal smooth muscle to epinephrine was studied by Youmans, Karstens and Aumann.<sup>35</sup> The only denervation which produced extreme hypersensitivity of the intestinal smooth muscle to epinephrine was that which involved sectioning of axons passing to the intestine from cell bodies located in the preautonomic ganglia.

The probability that both cholinergic and adrenergic effects may be noted simultaneously, possibly owing to central stimulation in the vicinity of the hypothalamic areas, receives further confirmation from the observations by Milhorat and his collaborators.<sup>36</sup> These authors carried out experiments in which they subjected the intestines of rabbits to venous blood of patients showing anxiety or fear. Unlike the effects of blood from normal controls, the specimens of blood taken during states of marked emotional disturbance caused definite changes in the motor activity of the intestinal muscle under study. These effects were not like the relatively simple response observed with epinephrine or acetylcholine in similar experiments, but were mixed in nature, generally tending to resemble those of cholinergic drugs. An interesting finding was that blood taken from psychotic patients in quiescent periods showed none of the effects on motor activity produced by blood taken from patients in an anxiety state. The mechanism underlying the motor, secretory and vascular changes visualized by Wolf and Wolff, which have already been referred to, may thus receive some experimental confirmation.

33 Mautner, H, and Yetwin, I J. Effects of Pentamethylenetetrazol (Metrazol) on the Stomach, *J Am Pharm A (Scient Ed)* **32** 17, 1943

34 Oppenheimer, M J, Glycer, N M, and Hamilton, R H. Intestinal Motility as Influenced Through Extrinsic Nerves as a Result of Central Stimulation by Bulbocapnine, *Proc Soc Exper Biol & Med* **51** 79, 1942

35 Youmans, W B, Karstens, A I, and Aumann, K W. Effect of Vagotomy and of Sympathectomy on the Sensitivity of Intestinal Smooth Muscle to Adrenalin, *Am J Physiol* **137** 87, 1942

36 Milhorat, A T, Small, S M, Doty, E J, and Bartels, W E. Probable Mechanism by Which Somatic Changes in Certain Emotional States Are Mediated, *Proc Soc Exper Biol & Med* **53** 23 1943

Emilsson <sup>37</sup> found that the l-isomers of adrianol, corbasil and synephrine always inhibited the rabbit intestine, while the d-isomers inhibited in large doses and stimulated in small doses. Other variations in the optical isomers of these drugs are discussed. The mechanism involved in the inhibition of intestinal motor activity is in part elucidated by the influence of sympathicolytic agents, such as bee venom and ergotamine, on the action of epinephrine substitutes. The same author <sup>38</sup> noted that the action of epinephrine and similar drugs in inhibiting intestinal activity is momentary and is completely abolished by a sufficient dose of bee venom or ergotamine, whereas drugs like amphetamine, whose inhibiting action develops slowly, are not abolished by such sympathicolytic agents. Amphetamine and similar drugs must produce their effect by direct muscular depression and not through action on the sympathetic nerve endings or specific receptors, as does the first group.

Youmans and his associates <sup>39</sup> studied the relation of the extrinsic nerves of the intestine to the inhibitory action of atropine and scopolamine. Atropine appears to exercise an inhibitory action on the tonus and rhythmic activity of the intestine independently of the extrinsic nerves. Its action is not reduced by vagotomy, and although sympathectomy results in an increased sensitivity of the intestine to the inhibitory action of the drug, it seems that the action of atropine is probably accomplished by a local action of the drug on the neural or muscular elements of the intestinal wall, in that it renders smooth muscle unresponsive to acetylcholine, which is being produced at a basal level in the intestine independently of the extrinsic nerves. The actions of scopolamine were indistinguishable from those of atropine. Studies on isolated intestinal loops by Shaw <sup>40</sup> indicate that the site of the depressant action of barbiturates on the intestine is in the postganglionic fibers and the muscle cells. This depressant action is abolished by physostigmine, there being a reciprocal antagonism between these two drugs.

Gernandt <sup>41</sup> has investigated the biologic activity of the P substance obtained by alcoholic extraction of rabbit or horse intestinal wall. This substance causes a transitory fall in blood pressure and considerable rise in intestinal motility. In vivo preparations of the P substance applied either locally or intravenously in rabbits produce movements of the small intestine but not of the colon and increase intestinal peristalsis. Another substance, indole, has been found by Garcia-Blanco and his associates <sup>42</sup> to have an inhibitory action on the rhythmic movements of the isolated rabbit intestine. With a 1 per cent concentration of indole such movements were suppressed, and when the substance was injected into the lumen of the intestine in a concentration of 0.017 per cent, movements ceased. Substitution of a hydrogen ion by a methyl, acetic or propionic radical made the substance inactive.

37 Emilsson, B. The Action of the Optical Isomers of Adrianol, Corbasil, Synephrine and Ephedrine on Isolated Intestine, *Acta physiol Scandinav* **3** 275, 1942.

38 Emilsson, B. Influence of Sympathicolytic Agents on the Action of Adrenaline Substitutes on Isolated Intestine. I. Bee Venom and Ergotamine, *Acta physiol Scandinav* **3** 335, 1942.

39 Youmans, W. B., Karstens, A. I., and Aumann, K. W. Relation of the Extrinsic Nerves of the Intestine to the Inhibitory Action of Atropine and Scopolamine on Intestinal Motility, *J Pharmacol & Exper Therap* **77** 266, 1943.

40 Shaw, F. H. The Action of Barbiturates on the Isolated Intestine, *Australian J Exper Biol & M Sc* **20** 117, 1942.

41 Gernandt, B. The Biological Activity of the P Substance, *Acta physiol Scandinav* **3** 270, 1942.

42 Garcia-Blanco, J., del Castillo, J., and Rodeles, F. J. Effect of Indol on Intestinal Motility, *Rev Soc argent de biol* **17** 473, 1941.

The mode of action of phenolphthalein has been studied by Blick, Barardi and Wozasek.<sup>43</sup> Intravenous injection of this drug in dogs did not increase peristaltic activity of the small intestine. Activity of the large bowel was increased, but there appeared to be no concomitant vagal action on the heart, a finding which would support the view that the action of phenolphthalein is not due to general parasympathetic stimulation. Comparison with other drugs which are known to stimulate intestinal activity is of interest. Phenolphthalein simulates the action of barium on the intestine, the latter, however, is much stronger in action on the muscle than is phenolphthalein and affects the heart muscle, whereas phenolphthalein does not. Solution of posterior pituitary, when applied locally, acts on the intestinal musculature even more markedly than phenolphthalein. Atropine, which inhibits the motor nerves of the intestine, does not stop the cathartic action of phenolphthalein. Physostigmine, which increases motor activity apparently by vagal stimulation, also has an effect on the heart rate. It would appear, therefore, that phenolphthalein acts directly on the muscle rather than on the autonomic nerve fibers.

An excellent summary of the important recent literature concerning intestinal motility is to be found in a review by Ingelfinger,<sup>44</sup> who discusses some seventy-three articles in adequate detail.

*Secretory Aspects*—The mechanism of gastric secretion has received considerable attention. The physiology of the parietal cells, with special reference to the formation of acid, is the subject of a discussion by Gray,<sup>45</sup> who presents the existing evidence bearing on the production of gastric acid. According to him this evidence indicates that the parietal cells of the stomach secrete an isotonic solution containing chlorine, hydrogen and potassium ions. The process of formation of acid is independent of external sources of carbon dioxide. Approximately 1.5 large calories of energy are required for the production of 1 liter of parietal secretion. The energy for secretion is probably supplied by the oxidation of dextrose. All the evidence discussed satisfies the requirements of the carbonic anhydrase theory of acid formation—namely, that the carbon dioxide formed within the parietal cell by its metabolic activity is converted immediately into carbonic acid by the activity of the enzyme carbonic anhydrase. The acid then ionizes, and the resulting hydrogen ions are diverted into the parietal secretion. At the same time the bicarbonate ions are sent into the blood in exchange for an equivalent amount of chloride ions, which are then also diverted into the secretion to complete the hydrochloric acid. Such a conception receives confirmation from Davenport,<sup>46</sup> who states that the conclusion that the parietal cells actually secrete isotonic hydrochloric acid should be accepted until overwhelming experimental evidence to the contrary is obtained. A detailed discussion of the present knowledge of this intricate subject is to be found in a second paper by the same author,<sup>47</sup> and a further consideration of the same problem, in which some additional points are mentioned, is included in an article by Hollander.<sup>48</sup> The latter recapitulates an extensive analysis of the literature and adds his own

43 Blick, P. Barardi, J. B., and Wozasek, O. The Mode of the Laxative Action of Phenolphthalein, *Am J Digest Dis* 9 292, 1942.

44 Ingelfinger, F. J. The Modification of Intestinal Motility by Drugs, *New England J Med* 229 114, 1943.

45 Gray, J. S. The Physiology of the Parietal Cell with Special Reference to the Formation of Acid, *Gastroenterology* 1 390, 1943.

46 Davenport, H. W. The Secretion of Water as a Component of Gastric Acid Secretion *Am J Digest Dis* 9 416, 1942.

47 Davenport, H. W. The Secretion of Acid by the Gastric Mucosa, *Gastroenterology* 1 383, 1943.

48 Hollander, F. The Chemistry and Mechanics of Hydrochloric Acid Formation in the Stomach, *Gastroenterology* 1 401, 1943.

observations and experiments. The essential characteristic of parietal secretion is that it is an isotonic, or slightly hypertonic, solution of hydrochloric acid, which may contain hydrobromic acid and hydriodic acid when their salts are present in the blood stream, but nothing else. The immediate source of chlorine lies in the neutral chlorides of the blood and lymph. The entire process of hydrochloric acid formation, starting with the blood chloride and ending with the ejection of acid into the gastric cavity, requires less than one minute. The hydrochloric acid is formed by hydrolysis of the neutral chlorides of the cytoplasm, the residual alkali being neutralized immediately by the intracellular buffers. Isotonicity is attained coincident with the transference of water and hydrochloric acid into the lumen of the gland. Thus the formation of the parietal secretion constitutes a "steady state" in which the concentrations of water and hydrochloric acid as they pass out of the cells are in a fixed ratio. Apparently the parietal cells are indefatigable as long as an adequate supply of water and chlorides is maintained. The process involves chemical, osmotic, electrical and mechanical work, but as yet there is no explanation for the mechanism by which the energy for such work is provided.

Epshtein<sup>49</sup> studied the changes and the chemical composition of the gastric juice caused by the administration of bromides. The administration of sodium bromide produced an increase in gastric secretion, an increase in the total and free acidity and an increase in the total content of the halogens, with a certain rise in the amount of liberated potassium, the concentration of which is greater in the more acid juices. If the gastric secretion is considered as a phenomenon of membrane equilibrium of the type of "steady state," it follows that the increase in the secretion is accompanied with a rise in the acidity of the gastric juice and in the content of precisely those elements which possess a greater mobility (potassium versus sodium, and bromide versus chlorine).

A somewhat new conception of gastric contents is presented by Cope, Cohn and Brenizer.<sup>50</sup> These authors studied the absorption of radioactive sodium and heavy water from pouches of the body and antrum of the dog's stomach. Radioactive sodium is absorbed in small but significant quantities from the body or acid-secreting areas. Two or three times as much is absorbed when the mucosa is resting as when it is in a secreting state. The gastric antrum absorbs one hundred times as much as the acid-secreting body. Variations in the osmotic pressure of the sodium solutions and in electrolyte concentrations in the blood serum would have no significant effect on the rate of absorption of the sodium. Observations on the absorption of heavy water ( $D_2O$ ) indicated that there was no significant difference in the rate of absorption between the body and the antral pouches, half of the heavy water being absorbed in approximately twenty minutes. The authors conclude that the conception that the fluid in an isolated pouch of the stomach represents secretion is obsolete and that the antrum plays a preponderant role in any observed absorption from the whole stomach. On the assumption that the gastric membrane handles heavy water as it does ordinary water, the authors conclude that there is a rapid exchange of the latter between the gastric contents and the body fluids, such an exchange would provide a major reason for isotonicity.

49 Epshtein, I. A. Distribution of Bromide in the Organism After the Administration of Br Salts, *Ark. biol. Nauk* **56** 59, 1939.

50 Cope, O., Cohn, W. E., and Brenizer, A. G., Jr. Gastric Secretion. II. Absorption of Radioactive Sodium from Pouches of the Body and Antrum of the Stomach of the Dog, *J. Clin. Investigation* **22** 103, 1943. Cope, O., Blatt, H., and Ball, M. R. Gastric Secretion. III. Absorption of Heavy Water from Pouches of the Body and Antrum of the Stomach of the Dog, *ibid.* **22** 111, 1943.

The great factor of safety in the blood supply of the stomach is exemplified by the experiments reported by Babkin, Armour and Webster<sup>51</sup> Ligation of most of the gastric arteries affected the secretory function of the stomach little, except that some transient diminution of the volume of gastric secretion was evoked by sham feeding or by subcutaneous administration of histamine Similar effects were noted in relation to the secretion of pepsin The acidity and the total chloride concentration of the gastric juice remained unchanged after partial or almost total devascularization of the stomach, and such arterial ligation never led to the formation of peptic ulcer or even of mucosal erosions Confirmation of these findings is to be seen in similar studies by Layne and Bergh,<sup>52</sup> who found that ligation of two or three of the large arteries supplying the stomach produced no significant alteration of acid gastric secretion in the dog and did not change the appearance of the gastric mucosa as viewed through the gastroscope When the four large arteries of the stomach were ligated, the animals died within six to thirty-six hours, as a result of necrotizing lesions Such observations demonstrate the existence of free and liberal anastomosis between the gastric, esophageal and phrenic arteries and indicate the safety with which ligation, within reason, may be practiced in surgical operations

The observations of Hoelzel<sup>53</sup> on himself suggest a relationship between the hydration of the body and gastric acidity With a diet high in protein and fat and low in carbohydrate and calories, the gastric secretion of hydrochloric acid was definitely reduced With such a diet, as the weight of the individual fell, so did the gastric acidity With increased calories taken as carbohydrate, the body weight rose, and hydration increased, as is well known, and with it the gastric acidity Such a finding may bear on the statement by Hollander, already alluded to, that the secretion of parietal cells is maintained as long as an adequate supply of water and chlorides is present

One of the most provocative contributions to the physiology of gastric secretion is that by Stefko, Andrus and Lord<sup>54</sup> These authors report the effects of jejunal transplants into the wall of the stomach on the free and combined acidity of the gastric secretion and the  $p_H$  of the various parts of the mucosa of the stomach The results of this procedure on gastric secretion consisted in a reversal of the normal response to histamine in most of the experimental animals The fasting  $p_H$  showed little change but the  $p_H$  level after administration of histamine was considerably elevated after the implantation of the jejunal segment The effect on the gastric analysis was similar, the average free and combined acidities during fasting being diminished after transplantation, and this decrease was accentuated by histamine These changes occurred within forty-five minutes after the transplantation and persisted for at least four months In 2 animals (dogs) the transplant was resected later and subsequent testing with histamine revealed normal reactions It was found that transplants from the ileum and the colon were without effect as

51 Babkin, B P , Armour, J C , and Webster, D R Restoration of the Function Capacity of the Stomach When Deprived of Its Main Arterial Blood Supply, *Canad M A J* **48** 1, 1943

52 Layne, J A , and Bergh, G S The Effect of Ligation of Arteries of the Stomach upon Acid Gastric Secretion and upon the Endoscopic Appearance of the Gastric Mucosa in the Dog, *Surgery* **13** 136, 1943

53 Hoelzel, F Gastric Acidity, Nutritional Hydration and Appetite, *Am J Digest Dis* **10** 121, 1943

54 Stefko, P , Andrus, W deW , and Lord, J W , Jr The Effects of Jejunal Transplants on Gastric Acidity, *Science* **96** 208, 1942 Lord, J W , Jr , Andrus, W deW , and Stefko, P Comparative Effects of Pedicle Grafts from Different Levels of Intestinal Tract on  $p_H$  of Gastric Mucosa, *Proc Soc Exper Biol & Med* **52** 100, 1943

regards any influence on the  $p_H$  of the gastric mucosa after injection of histamine. On the other hand, with both duodenal and jejunal grafts, the  $p_H$  of the mucosa rose after the administration of histamine, the jejunal grafts being somewhat more effective. Such experimental findings are of the utmost importance, and the implication is clear. It is obvious that the depression of gastric secretion was evoked by some hormonal stimulation rather than by the actual amount of neutralizing substance secreted by the transplant. Whether this effect was through some medium such as enterogastrone remains to be determined, but the findings are of extreme significance inasmuch as they suggest an entirely new and apparently physiologic approach to the treatment of peptic ulcer. Jejunal transplants in human patients with ulcer have already been performed as a result of these experiments, but sufficient time has not elapsed to warrant conclusions as to the validity of such a surgical procedure.

Further evidence of the hypothetic gastric secretory hormone, gastrin, is to be found in reports by Komarov<sup>55</sup>. An apparently specific secretagogue can be consistently extracted from the pyloric mucosa of the dog and of the hog by methods previously described. The pyloric extracts were so purified that they stimulated a secretion of highly acid gastric juice virtually devoid of peptic power but had no effect on pancreatic or biliary secretion, did not influence blood pressure, had no toxic effects and were free from histamine. The results were not abolished by atropine, vagotomy or splanchicectomy.

Scott, Moe, and Brunschwig<sup>56</sup> have made further studies on the properties of the gastric secretory depressant found in gastric juice. In patients with achlorhydria, gastric cancer or pernicious anemia this factor is present in relatively high concentration. It is contained in the flocculent precipitate obtained by the addition of four volumes of absolute alcohol to neutralized gastric juice. Investigation has shown that the method used for extraction of the gastric secretory-depressant factor from urine (urogastrone) does not extract the gastric secretory depressant from an alcohol precipitate of human gastric juice, hence these two factors are not identical. Urogastrone has been further studied by Schiffrin and Gray<sup>57</sup> in enterectomized dogs, in order to obtain further evidence that it is not identical with enterogastrone. Their experiments were carried out in animals in which the entire small intestine, from the pylorus to the ileocecal sphincter, was removed, together with excision of the body of the pancreas and ligation of the common duct. Urogastrone effectively inhibited the volume of gastric secretion and the output of free acid. Similar results were obtained in dogs with vagotomized total gastric pouches. No evidence was obtained that urogastrone inhibits gastric secretion through the liberation of enterogastrone.

Attempts to determine the relationship of the neurohypophysis to gastric secretion were made by Gross and his collaborators<sup>58</sup>. Section of the pituitary stalk in dogs resulted in a high degree of polyuria but no alteration in the acidity of the gastric juice. The injection of pitressin tannate into dogs with normal gastric pouches produced no alteration in either volume or acidity.

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55 Komarov, S. A. Studies on Gastrin. II. Physiological Properties of the Specific Gastric Secretagogue of the Pyloric Mucous Membrane, *Rev. canad. de biol.* **1** 377, 1942.

56 Scott, V. B., Moe, R., and Brunschwig, A. Further Studies on the Properties of the Gastric Secretory Depressant in Gastric Juice, *Proc. Soc. Exper. Biol. & Med.* **52** 45, 1943.

57 Schiffrin, M. J., and Gray, J. S. The Effect of Urogastrone on Gastric Secretion in Enterectomized Dogs, *Am. J. Physiol.* **137** 417, 1942.

58 Gross, E. G., Ingram, W. R., and Fugo, N. W. Experiments on the Relationship of the Neurohypophysis to Gastric Secretion, *Am. J. Digest. Dis.* **9** 234, 1942.

The multiplicity of factors entering into the various phases of gastric digestion alone is indicated in the detailed studies of Ohlsen<sup>59</sup> on the distribution of enzymes in various parts of the gastric mucosa, as studied by histochemical methods. Diaminopeptidase and aminopolypeptidase are distributed independently of each other in the pyloric and fundic mucosa. The former is predominant in the region of the pit epithelium and the neck of the chief cells, while the latter is found predominantly in the chief cells of the fundus. Pepsin is the characteristic enzyme to be found in the fundus and follows the distribution of the chief cells. Dipeptidase, aminopolypeptidase and prolinpeptidase almost alone characterize the pyloric mucosa, and in man abundant urease occurs in the surface mucosa in the region of the pylorus.

It is now generally accepted that pepsin and rennin are distinct and different enzymes, and the impression is that they are both present in gastric juice. Dotti and Kleiner,<sup>60</sup> by ingenious experiments on human beings, have arrived at the conclusion that no rennin is present in the gastric juice of human adults.

Various factors influencing gastric secretion have been further studied. For example, Pincus and his associates<sup>61</sup> conclude that the introduction of acid into the duodenum inhibits gastric secretion only if a threshold level of duodenal  $p_H$  (approximately 2.5) is attained, and that the extent of depression of gastric secretion is dependent on the level of  $p_H$  produced. One might well ask whether such changes in the duodenal  $p_H$  coincide with the production of enterogastrone. Bantin<sup>62</sup> noted a temporary secretory alteration in gastric activity following ligation of the ductus choledochus that accompanied the inhibition of gastric motility already alluded to. A few days after the tying of the duct, the quantity of the gastric juice increased, together with the hydrochloric acid content and the digestive power of the gastric juice. This temporary increase was followed by depression of the quantity, quality and effectiveness of the gastric juices.

The secretion of acid by the stomach is greatly increased by the subcutaneous injection of benzylimidazoline (priscol). Thiele<sup>63</sup> notes that the subcutaneous injection of this preparation is followed by a more constant and satisfactory result than the ordinary test meal or the use of caffeine products, but that it is apparently somewhat inferior to histamine. Unlike histamine, however, it causes no disturbing side reactions and can be given in several successive 10 mg. doses.

In addition to its effect on motor activity, the effect on gastric secretion of the histamine antagonist thymoxyethyldiethylamine (929 F) has been observed. Bourque and Loew<sup>64</sup> carried out experimental studies on this preparation, as well as on a similar histamine antagonist, N-phenyl-N-ethyl, N'-diethylethylenediamine (1571 F), using as stimulants to secretion histamine, pilocarpine and food. The data from these studies on dogs with gastric pouches did not support the belief that 1571 F is a specific antagonist to histamine, and although the drug reduces gastric secretion following stimulation with histamine in dogs with gastric pouches,

59 Ohlsen, A. S. Contribution to the Histochemistry of the Stomach, *Compt rend d trav du lab Carlsberg, serie chim* **23** 329, 1941.

60 Dotti, L. B., and Kleiner, I. S. Absence of Rennin from Adult Human Gastric Juice, *Am J Physiol* **138** 557, 1943.

61 Pincus, I. J., Thomas, J. E., and Rehfuess, M. E. A Study of Gastric Secretion as Influenced by Changes in Duodenal Acidity, *Proc Soc Exper Biol & Med* **51** 367, 1942.

62 Bantin, E. V. Retention of Gall and Its Effect on the Activity of the Stomach, *J Physiol USSR* **27** 599, 1939.

63 Thiele, W. Priscol, a New Substance for Gastric Diagnosis, *Klin Wchnschr* **19** 620, 1940.

64 Bourque, J. E., and Loew, E. R. Effect of Histamine Antagonists on Gastric Secretion, *Am J Physiol* **138** 341, 1943.



the reduction in secretion was nearly identical after stimulation with pilocarpine. This drug did not modify gastric secretion in dogs with gastric pouches stimulated with food. Pretreatment with 929 F failed significantly to modify the secretion from gastric pouches in dogs given injections of pilocarpine.

Injections of "prolan" into dogs decreased the secretion of the stomach juice after a standard meal, according to Eidinova.<sup>65</sup> The depression was most manifest on the fourth and fifth days after administration of the drug. Parrot<sup>66</sup> found that in dogs epinephrine markedly activates gastric secretion. Under the influence of diverse sympatholytic agents, such as yohimbine and ergotamine, the volume of secretion is increased 30 to 150 per cent compared with control levels. Activation of this secretion is inhibited by atropine. The question whether histamine and acetylcholine are brought into play after injection of epinephrine was studied. The secretion following injection of histamine differs from that produced by epinephrine in that latency time is shorter, the juice is less rich in nitrogenous substances and the secretion is not abolished by atropine.

According to Stavraký,<sup>67</sup> mecholyl causes a secretion of alkaline mucus from the pyloric portion of the stomach simultaneously with the secretion of acid and pepsin from the fundic pouch. From the whole stomach, fractionated injections of mecholyl cause abundant secretion of acid, whereas single doses of mecholyl cause only a scanty secretion of gastric juice of low acidity. The concentration of pepsin in the gastric juice is high as long as the secretion is acid in reaction. The concentration of pepsin is independent of the volume of secretion or of the mode of administration of mecholyl, but is directly related to the amount of mecholyl given. Preceding administrations of mecholyl also raise the concentration of pepsin in the gastric juice evoked by stimulation of the vagi.

Because of differences of opinion concerning the secretion of gastric juice during the interdigestion period, Mears<sup>68</sup> made observations on a group of approximately normal persons and on a group of patients with ulcer. Gastric secretion during the night was observed by means of indwelling nasal tubes. During control periods mean values indicated that the secretory rate and the volume of secretion of free and of total acid were higher for the group with ulcer than for the control group. This, of course, conforms with the usual conception of gastric secretion in patients with ulcer. Atropine diminished the volume of secretion as well as the free and total acidity in both the normal group and the patients with ulcer. It is interesting to note that the decrease in these values was more pronounced in the group with ulcer.

Inhibition of peptic activity was studied by Shoch and Fogelson.<sup>69</sup> These authors demonstrated that mucin, magnesium trisilicate and aluminum hydroxide inhibited the peptic activity of gastric juice by decreasing the acidity, the amount of inhibition being directly related to changes in  $p_H$ . Sodium lauryl sulfate completely inhibited peptic activity, regardless of  $p_H$ , through its protein-denaturing action. The use of this substance (as Dreft) has been somewhat too widely publicized, but the inactivation of gastric pepsin by detergents should be thoroughly

65 Eidinova, M. L. The Influence of Hormones on the Excitability of the Digestive Glands, *J. Physiol. USSR* **28** 354, 1940.

66 Parrot, J.-L. Action sécrétoire de l'adrénaline sur l'estomac. Longue durée du temps de latence. Hypothèse sur le mécanisme de cette action, *Compt. rend. Acad. d. sc.* **212** 1054, 1941.

67 Stavraký, G. W. Some Aspects of Gastric Secretion Induced by Mecholyl, *Canad. M. A. J.* **48** 68, 1943.

68 Mears, F. B. The Effect of Atropine on Gastric Secretion During the Night, *Surgery* **13** 214, 1943.

69 Shoch, D., and Fogelson, S. J. Peptic Inhibition, *Proc. Soc. Exper. Biol. & Med.* **50** 304, 1942.



investigated in man because of the possible application of such a principle to the therapy of ulcer.

The effectiveness of replacement therapy for achlorhydria has long occasioned serious doubts. The actual amount of any acid necessary to bring the  $p_H$  of the gastric contents following a normal meal to physiologic range ( $p_H$  1.6 to 1.8) or for peptic activation (below  $p_H$  2.0) is of such magnitude that practical aspects preclude its administration. Koehler and Windsor<sup>70</sup> have carried out in vitro experiments with a normal meal, rather than an Ewald test meal, and arrive at this conclusion. For achlorhydric patients ingesting a normal meal, the amount of U.S.P. hydrochloric acid needed to bring about optimum  $p_H$  values would be approximately 35 cc. Even twenty 420 mg capsules of glutamic acid hydrochloride with a meal would fail to produce normal activity or to activate pepsin. If such findings are correct, it is obvious that the administration of hydrochloric acid therapeutically to patients with achlorhydria must have some other effect than that of acidifying gastric contents or activating pepsin.

Anacidity has little or no effect on the absorption of ascorbic acid, as shown by Chernya.<sup>71</sup> The urinary excretion of vitamin C in anacid patients corresponds to that in patients with normal secretions, and it would appear that the daily requirement of vitamin C in anacidity is about the same as that in other gastric diseases or in the normal state. That this is true is indicated by the report of Acharkan and Borinskaya,<sup>72</sup> who studied the maintenance of ascorbic acid saturation in patients with ulcer. These investigators found that no larger amounts were required to maintain saturation than in normal persons, and they noted at the same time that the amount of ascorbic acid in the gastric juice increases correspondingly to the increase of its concentration in the blood.

The measurement in situ of the  $p_H$  of the antral and pyloric portions of the stomach and the duodenum has been done by means of a special intragastric electrode. Breuhaus and Eyerly<sup>73</sup> have previously contrasted in situ  $p_H$  values with those obtained by aspiration and found that marked differences were not uncommon. The present investigation was aimed at a comparison of the in situ  $p_H$  values of the antrum of the stomach, pylorus and duodenum of normal subjects with those of patients with duodenal ulcer and achlorhydria. Normal persons and patients with ulcer had essentially the same fasting gastric  $p_H$  values and stimulation with histamine produced a lower gastric  $p_H$  in normal subjects than in patients with ulcer. The alternation of administration of an antacid with milk and cream feedings raised the  $p_H$  of the stomach, pylorus and duodenum more than half-hour feedings alone. In patients with achylia, the gastric reaction was mildly acid. Milk and cream feedings or a combination of such feedings with administration of antacids lowered the gastric and duodenal  $p_H$  of patients with pernicious anemia below that found in the fasting state. The duodenal reactions of normal persons and of patients with ulcer and with achylia tended to remain mildly acid. On the basis of these studies, the authors attempt to invoke an acid mechanism other than that of the secretion of hydrochloric acid, but it is quite possible that careful electrolyte studies of the gastric contents would not confirm their suggestion.

70 Koehler, A. E., and Windsor, E. The Effectiveness of Replacement Therapy in Achlorhydria, *Ann. Int. Med.* **18** 182, 1943.

71 Chernya, Y. M. Vitamin C and the Secretory Insufficiency of the Stomach, *Vopr. pitan.* **10** 27, 1941.

72 Acharkan, A. I., and Borinskaya, E. N. Study of C-Vitamin Balance in Ulcerous Patients, *Vopr. pitan.* **10** 22, 1941.

73 Breuhaus, H. C., and Eyerly, J. B. In Situ  $p_H$  of the Antrum of the Stomach, Pylorus and Duodenum, *Gastroenterology* **1** 583, 1943.

that acid other than hydrochloric acid influences the  $p_H$  of the upper part of the gastrointestinal tract

Studies of gastric secretion in the newborn infant are of some interest. Ritter<sup>74</sup> shows that the stomach of the newborn infant exhibits a high secretory capacity, with figures that suggest hypersecretion, as judged by adult standards. An appreciable number of infants in his study showed a lack of free hydrochloric acid, which he thinks may be a significant factor in the development of anemia and rickets in infants, in spite of an adequate intake of iron, calcium and vitamin C. Miller<sup>75</sup> carried out studies on secretion of gastric acid during the first year of life, and his studies confirmed Cutter's results, that there is a rapid increase in gastric acidity during the first year of life. Without histamine, he showed that there is a rapid increase in the concentration of gastric hydrochloric acid during the first twelve months, with a probable increase in volume, and at the end of this period the reaction of the stomach to a test meal closely resembles that of an adult. Accompanying the development of the digestive power of the stomach, there is a diminution in the number of achlorhydric infants.

Methods for studying digestive activity in the intestinal tract are time consuming and as a rule permit only approximate results. Studies by Berger and Oppenheim<sup>76</sup> on the drainage output from the human duodenum indicate that effective duodenal drainage can be achieved without the use of an obstructing balloon. This was accomplished by providing optimum suction, which permitted the removal of practically all of the secretion. Simultaneous drainage of the duodenum and jejunum under these conditions showed that the escape of fluid during an adequate duodenal drainage was negligible (0 to 4 per cent). Employment of this technic, if successful, would simplify the study of the collection of duodenal contents but would not preclude its dilution by gastric juice.

An ingenious method of determining the digestive activity in any portion of the human digestive tract is presented by Elsom and his associates.<sup>77</sup> The food substance to be digested is placed in a fenestrated metal cylinder that is housed in an outer cylinder which protects the contained material from the digestive tissues. The apparatus is introduced to any desired level of the digestive tract by intubation, and when desired the fenestrated cylinder is partially ejected from its housing by air pressure, the test substance thus being exposed to the intestinal juice. The amount of material lost by digestion in a measured period is determined chemically. A few illustrative results are given in the article, but the value of the method for studying digestive processes in various diseases awaits application.

The presence of alkaline phosphatase in the small intestine has been recognized for many years, but little attention has been paid to the phosphatase activity of the intestinal secretions. This particular phase of intestinal secretion was studied by Kosman and his associates<sup>78</sup> at various levels of the intestinal tract. The results of the studies indicated that the phosphatase activity of the duodenal,

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74 Ritter, J. A. Fractional Gastric Analysis in the Newborn. Preliminary Report, *Pennsylvania M. J.* **44** 1321, 1941.

75 Miller, R. A. Gastric Acidity During the First Year of Life, *Arch. Dis. Childhood* **17** 198, 1942.

76 Berger, W. V., and Oppenheim, E. Drainage Output from the Human Duodenum. Extrinsic Factors Influencing Drainage, *Gastroenterology* **1** 285, 1943.

77 Elsom, K. A., Chornock, F. W., and Dickey, F. G. A Method of Determining the Digestive Activity in any Portion of the Human Gastrointestinal Tract. Some Measurements of Protein Digestion in the Stomach and Small Intestine, *J. Clin. Investigation* **21** 795, 1942.

78 Kosman, A. J., Kaulbersz, J. W., and Freeman, S. The Secretion of Alkaline Phosphatase by the Dog's Intestine, *Am. J. Physiol.* **138** 236, 1943.

jejunal and ileal contents obtained from enterostomized dogs after various test meals showed the greatest activity after protein and fat meals and the least after a carbohydrate meal. Large quantities of phosphatase were obtained in the secretions of isolated intestinal loops. The degree of activity of various segments of the intestinal tract was diminished from above downward, the duodenum and jejunum containing the greatest concentration of phosphatase in the secretions and the colon the least. The distribution of alkaline phosphatase in the different parts of the alimentary tract, as shown by tissue stains, was studied by Bourne,<sup>79</sup> whose findings agree with the results obtained by other workers. In relation to the phenomenon of phosphorylation, he points out the important fact that the presence of phosphatase in the brush borders of cells in those parts of the alimentary tract where most active absorption can take place, i. e., the duodenum, jejunum and rectum, is in partial contrast to the absence of a reaction in the epithelial cells in those parts of the tract which are not important centers of absorption, i. e., the stomach and colon.

*Absorptive Aspects*—The complex phenomenon of absorption from the gastrointestinal tract still includes many unexplained processes. Phosphorylation remains somewhat of a hypothesis, but continued studies contribute to its further elucidation. Iodoacetic acid, which prevents phosphorylation, has been reported to diminish absorption of the three hexoses, dextrose, fructose and galactose. Since iodoacetic acid is toxic, conclusions from such experiments have doubtful value. By the use of phlorhizin, more reliable deductions are possible, and studies on the organic phosphate and "fructose" in the rat intestinal mucosa as affected by dextrose and phlorhizin have been made by Beck.<sup>80</sup> Increases in nonpyrophosphate organic phosphorus in compounds reacting like fructose were much smaller in rats fed dextrose and phlorhizin than in rats fed dextrose only. No significant difference was found in pyrophosphate organic phosphate, and such a finding supports the position that active absorption of dextrose, fructose and galactose proceeds through phosphorylation.

Bellini and Cera<sup>81</sup> studied the behavior of the glycerophosphatases of the intestine during intestinal resorption of glycerophosphate. The glycerophosphatase content of the intestinal mucous membrane of fasting rats was determined, after which sodium glycerophosphate was injected into a section of the intestine which was tied off toward the stomach. Four hours after the injection the glycerophosphatase content of the intestinal mucous membrane had been reduced about 40 per cent, while at the same time the injected ester was hydrolyzed. The rate of absorption of dextrose from the intestine was studied in rats by Pauls and Drury<sup>82</sup> in the presence of diabetes. Depancreatized rats were used. Under such conditions, even on a high carbohydrate diet, the animals lost large amounts of dextrose daily in the urine and consumed correspondingly large amounts of food. The diabetic rats appeared to store sugar with difficulty and on a high carbohydrate diet consumed large amounts of sugar. Even assuming that the intestinal absorption of dextrose proceeded at the same rate throughout the day and night, the

79 Bourne, G. The Distribution of Alkaline Phosphatase in Various Tissues, *Quart J Exper Physiol* **32** 1, 1943.

80 Beck, L. V. Organic Phosphate and "Fructose" in Rat Intestinal Mucosa, as Affected by Glucose and by Phlorizin, *J Biol Chem* **143** 403, 1942.

81 Bellini, L., and Cera, B. The Behaviour of the Glycerophosphatases of the Intestine During Intestinal Resorption of Glycerophosphate, *Biochim e terap sper* **27** 146, 1940.

82 Pauls, F., and Drury, D. R. The Rate of Glucose Absorption from the Intestine of Diabetic Rats, *Am J Physiol* **137** 242, 1942.

absorption coefficients were extremely high, indicating that the absorption mechanism of the intestinal tract under these circumstances operates efficiently

The absorption of fat from the gastrointestinal tract was studied by Rekers, Abels and Rhoads<sup>83</sup> The subjects studied included 2 normal persons and 1 patient with gastric cancer, 1 with a total gastrectomy, 1 with generalized atrophic gastritis and 2 with hepatic cirrhosis An abnormal absorption of fat was demonstrated only in the gastrectomized patients and in the patient with atrophic gastritis This is of interest as indicating that hepatic dysfunction apparently plays no constant significant role in the absorption of gastrointestinal fat Fluoroscopic studies proved that increased intestinal motility was not a causative factor for the steatorrhea The authors consider the possibility that the proper absorption of lipids is influenced by the presence of a normal functioning gastric mucosa, since both the patient with severe gastric atrophy and the one entirely lacking a stomach suffered from a decreased efficiency of fat absorption

An attempt to illustrate absorption of fat is to be found in the experiments of van Weel,<sup>84</sup> who determined the distribution of dipeptidase and maltase in the small intestine by the use of histochemical micromethods The distribution of dipeptidase indicated that a synthesis of this enzyme might occur in the cells of Paneth Comparison of the results on enzymes in the duodenum and ileum in the small intestine of rats indicates a concentration of maltase in the crypts of Lieberkuhn and secretion of the enzyme by the secretory cells The author explains the resorption of fats by a splitting of the larger molecules into small particles and a resynthesis of the specific fats in the cells

The interrelation of calcium and fat utilization in the growing rat was studied by French<sup>85</sup> Balance experiments were conducted on young male rats, and with adequate synthetic diets the utilization of calcium decreased moderately and consistently in the order of the increasing fat content of the diets from 5 to 28 per cent and decreased considerably for the 45 per cent fat diet The intestinal contents were more acid with the 5 per cent fat diet than with those richer in fat The most efficient utilization of calcium accompanied the most acid reaction At least two factors seemed to be involved in the physiologic relationship between fat and calcium utilization (1) the acidity of the intestinal tract and (2) the formation of readily absorbable bile-fatty acid-calcium complexes

By means of a perfusion method, Numoto<sup>86</sup> determined the absorption of water in the ileum, ascending colon and rectum of rabbits, using 15 cm lengths of intestine The absorption averaged 11.5 cc per hour in the ileum, 15.6 cc per hour in the ascending colon and only 4.4 cc per hour in the rectum Various solutions of sodium chloride, sodium sulfate and magnesium sulfate showed no essential differences in their effects on water absorption, which depended essentially on the tonicity of the solutions According to the degree of absorption of water by the small intestine, solutions of these salts can be arranged in the following decreasing order: sodium chloride, sodium sulfate and magnesium sulfate

83 Rekers, P. E., Abels, J. C., and Rhoads, C. P. Metabolic Studies in Patients with Gastrointestinal Cancer. IV. Fat Metabolism, a Method of Study, *J. Clin. Investigation* **22** 243, 1943

84 van Weel, P. B. Histophysiology of the Small Intestine. III. Changes in the Glands of the Small Intestine During Digestion and During the Absorption of Fat, *Ztschr. f. Zellforsch. u. mikr. Anat.* **29** 751, 1939

85 French, C. E. The Interrelation of Calcium and Fat Utilization in the Growing Albino Rat, *J. Nutrition* **23** 375, 1942

86 Numoto, I. A Method for the Description of Intestinal Movements in Situ and Water Absorption in the Rabbit Intestine, *Okayama-Igakkaï-Zasshi* **51** 1110, 1939

Nicolai<sup>87</sup> found in earlier experiments that the absorption of phenol from the isolated jejunum of the rat showed a break in the time curve of the amount absorbed, i.e., at a certain point the amount of phenol in the intestine underwent a transitory increase instead of a decrease. This was interpreted as a protective function through which the poison was removed, even though only momentarily, from the body. In new experiments on animals whose jejuna had been irritated by the administration of castor oil and croton oil, this break in the curve was no longer evident, a finding that suggested a lowered protective function of the intestinal wall in the presence of an inflammatory process. Somewhat similar observations on the storage of indole in the intestinal wall following its absorption showed that in normal animals and in animals with an experimental fresh enteritis the initial storage of indole was about identical. The concentration in the intestinal wall, however, fell rather rapidly, reaching a zero value at the end of forty-five minutes, as compared with a constant value during sixty minutes in the normal animals. In a more chronic form of intestinal irritation, the amount stored in the intestinal wall reached a much lower initial level than in the normal animals or in those with a rather acute form of intestinal irritation and fell to zero within thirty minutes.

Dille and Whatmore<sup>88</sup> report data on the absorption of lanatoside C from the gastrointestinal tract of cats, comparing it with the absorption of tincture of digitalis. Lanatoside C is a crystalline glucoside isolated in mechanically pure form from digitalis lanata. The greatest absorption of lanatoside C and of tincture of digitalis USP XI takes place in the intestine, but quantities are also absorbed from the colon and stomach. The crystalline glucoside is absorbed more rapidly from the intestine than the tincture of digitalis. The studies show that partial destruction or inactivation of both substances takes place in the lumen of the gastrointestinal tract. Peterson and Finland<sup>89</sup> determined the absorption and excretion of a single dose of a sulfonamide drug in normal human subjects after oral and duodenal administration, and in addition, the effects of a meal, of the simultaneous administration of sodium bicarbonate and of the administration of a sulfonamide compound in the form of the sodium salt. A 5 Gm dose of sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine was used. The fluid intake was kept at a constant level. It was found that sulfanilamide was absorbed rapidly and completely when given orally or into the duodenum. Food delayed absorption but did not diminish the amount excreted in the urine. Sulfapyridine, sulfathiazole and sulfadiazine were poorly absorbed from the duodenum, and sulfadiazine was absorbed more slowly when given after a meal than when given during fasting. Alkali appeared to increase the amount of the drug absorbed when given with sulfadiazine after a meal. Sodium bicarbonate hastens the absorption of sulfadiazine when given during fasting but does not increase the amount absorbed, and sodium sulfadiazine is rapidly absorbed from the duodenum or after oral administration in a fasting subject, but absorption is delayed and less complete if it is given after a meal.

87 Nicolai, H. Quantitative Absorption Studies with Pure Intestinal Poisons. III. Phenol Absorption in the Small Intestine of Enteritic Rats, *Klin Wchnschr* 20 80, 1941.

88 Dille, J. M., and Whatmore, G. B. Gastrointestinal Absorption of Lanatoside C, *J Pharmacol & Exper Therap* 75 350, 1942.

89 Peterson, O. L., and Finland, M. The Effect of Food and Alkali on the Absorption and Excretion of Sulfonamide Drugs After Oral and Duodenal Administration, *Am J M Sc* 204 581 1942.

Factors affecting the absorption of sodium dl-mandelate from the intestine of cats were studied by Garry and Smith<sup>90</sup> From the small intestine and from the colon in decerebrated cats, there was slight but unequivocal preferential absorption of the laevo form of mandelic acid Such preferential absorbing power was not shown during ether or chloroform anesthesia was absent from intestines kept alive in vitro and did not survive in the intestines of cats recently killed The selective absorbing power seemed to be associated with the integrity of the intestinal epithelium

The selective absorption of botulinum toxin was studied by Dack and Hoskins<sup>91</sup> Amounts of botulinum toxin type A which were lethal when fed to 2 monkeys were without effect when injected into the colons of 4 others In a second experiment, large doses of toxin were injected into the colons of 3 surviving monkeys and botulism developed in only 1 The fourth surviving monkey served as a control and was given toxin orally It showed symptoms of botulism within twenty-four hours A discussion of these results is given concerning the relation of the permeability of the colon to toxin and the delayed symptoms sometimes occurring in patients with botulism.

Studies on the absorption of various iron preparations is to be found in a report by Labarre<sup>92</sup> Iron apparently is absorbed by the capillary vessels of the intestinal mucosa, not by the lymphatics It was found that better absorption of iron is obtained following the use of phosphogluconate of iron than from ferrous sulfate, pills of ferrous carbonate or iron and ammonium citrates The greater absorption of this iron salt is due to the fact that it is very soluble in water, that it is combined in a bivalent state, and that a 2 per cent solution of the salt has a  $p_H$  of 6.2 which corresponds to the  $p_H$  of the duodenum where most absorbable iron passes into circulation

#### CLINICAL ASPECTS

*Thoracic Pain and Disturbances in the Upper Part of the Digestive Tract*—The interpretation of pain arising from gastrointestinal lesions is sufficiently difficult to warrant attention to any articles contributing further light on the mechanism of its production and the course of its transmission Harrison<sup>93</sup> discusses puzzling aspects of pain in the chest and describes in particular certain gastrointestinal conditions which may be sources of diagnostic error The occasional occurrence of thoracic pain secondary to duodenal ulcer is illustrated by careful histories This is a rather unusual manifestation, and Harrison emphasizes the diagnostic importance of the circumstances under which pain occurs, as well as the actual location where the pain is perceived He mentions thoracic pain due to cascade stomach, which may produce an abnormal degree of spasm between the cardia and the body of the stomach, and in addition cites instances of angina-like pain secondary to diverticulum of the stomach With the latter there seems to be no relation to effort but a definite relation to meals, and the clinical picture is not unlike that associated with esophageal hiatus hernia

Alvarez<sup>94</sup> cites one of the important points made by Wolf and Wolff in regard to the production of gastric pain Pain resulted from distention of the coats of

90 Garry, R. C., and Smith, I. A. Factors Affecting Absorption of Sodium dl-Mandelate from the Intestine of Cats, *J. Physiol.* **101**:484, 1943

91 Dack, G. M. and Hoskins, D. Absorption of Botulinum Toxin Through the Colon of *Macaca Mulatta* *J. Infect. Dis.* **71**:260, 1942

92 Labarre, J. Absorption and Hematimic Action of Ferrous Phosphogluconate *Ferrex*, *Rev. canad. de biol.* **1**:104, 1942

93 Harrison, T. R. Some Puzzling Aspects of Pain in the Chest, *J. A. M. A.* **120**:519 (Oct. 17) 1942

94 The Production of Pain in the Stomach, editorial, *Gastroenterology* **1**:615, 1943

the stomach or from the force of an unusually vigorous gastric contraction. Neither the threshold nor the intensity of the pain experienced was altered by varying the area of gastric wall stimulated. Pricking or pinching the mucosa or application of strong faradic stimuli or strong acid failed to cause pain, unless at the time the gastric mucous membrane was congested and edematous. The latter point in particular is of extreme importance and, as Alvarez points out, agrees with observations made years ago by Ivy. It may well explain why ulcers are sometimes painful and at other times not.

A partial anatomic explanation for the unusual distribution of pain arising from gastric stimulation may be found in the studies of Balchum and Weaver.<sup>95</sup> It is now generally recognized that esophageal or gastric pain may at times simulate that of angina pectoris, even to its radiation down the arm. Although the experiments of these investigators were performed on dogs and are therefore subject to a certain amount of skepticism, it is of extreme interest that objective signs of pain following distention of the stomach were shown to be independent of the vagus and phrenic nerves and of the anterior roots of the thoracic and lumbar spinal nerves. Evidence is presented which indicates that some of the visceral afferent fibers involved in the mediation of pain that follows distention of the stomach are contained within the greater splanchnic nerve. These fibers traverse the rami communicantes of the eighth through the thirteenth thoracic spinal nerve, entering the spinal cord through the corresponding posterior roots. Some of these fibers seem to traverse the sympathetic trunk as far cephalad as the fourth thoracic. If these findings are correct and are applicable to human beings, such an anatomic distribution would go far toward explaining the anginal distribution of gastric and esophageal pain.

A careful discussion of the differential diagnosis of angina pectoris, with special reference to esophageal spasm and coronary occlusion, is contained in an article by Wolferth and Edeiken.<sup>96</sup> The authors divide the differential diagnosis of angina pectoris into two parts: differentiation from seizures of noncardiac origin and differentiation from acute coronary occlusion. In their opinion, esophageal spasm is of major clinical importance. They state that with "anginal" pain due to esophageal spasm there is a history of difficulty in swallowing during an attack and glyceryl trinitrate fails to relieve the pain, which may respond to antispasmodics, sedatives and psychotherapy. The electrocardiogram is not altered during attacks. There are many who would disagree with the statement that glyceryl trinitrate does not relieve esophageal spasm and pain resulting therefrom, but it is true that as a rule a careful history will differentiate between the substernal pain due to coronary heart disease and that due to esophageal or gastric disorders. In this connection, it is proper to refer to an article by Levy and Boas,<sup>97</sup> who present for consideration angina pectoris and the syndrome of peptic ulcer. These authors point out that the symptoms of peptic ulcer and angina may occur suddenly and simultaneously, and occasionally acute peptic ulcer may be associated with coronary thrombosis. Repeated attacks of angina at rest, finally eventuating in coronary thrombosis, may occur two or three hours after meals and during the night,

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95 Balchum, O. J., and Weaver, H. M. Pathways for Pain from the Stomach of the Dog, *Arch Neurol & Psychiat* **49** 739 (May) 1943.

96 Wolferth, C. C., and Edeiken, J. The Differential Diagnosis of Angina Pectoris with Special Reference to Esophageal Spasm and Coronary Occlusion, *Pennsylvania M. J.* **45** 579, 1942.

97 Levy, H., and Boas, E. P. Angina Pectoris and the Syndrome of Peptic Ulcer, *Arch Int Med* **71** 301 (March) 1943.



characteristic of pain from ulcer. When symptoms of angina and ulcer coexist, successful therapy for ulcer may cause remission of the anginal syndrome. The authors present 14 case histories and offer a detailed explanation of the phenomena just mentioned, which are largely based on the old theory of a vagovagal reflex. It should be stated that such instances are of extreme interest but are uncommon, inasmuch as the vast majority of patients with ulcer do not have associated coronary disease or coronary symptoms, as pointed out previously by White and his collaborators.

*Esophagus*.—Esophageal tumors which do not involve the mucosa are rare. Schatzki and Hawes<sup>98</sup> report a small group of intramural esophageal tumors and describe in detail the important diagnostic features to be noted by the roentgenologist. Gastrointestinal hemorrhage from esophageal polyps is extremely rare. Such an occurrence is described by Dickes and his associates,<sup>99</sup> who report a case of multiple polyps of the esophagus causing intermittent bleeding. Diagnostic proof rested on repeated esophagosopic examinations. Pennes<sup>100</sup> adds a report of a case of leiomyosarcoma involving the middle and lower thirds of the esophagus to the 5 cases previously noted in the literature.

The incidence of successful esophageal surgical operation for malignant or benign tumors is still increasing, due largely to the results of transthoracic procedures. Interesting reports are those of Brock,<sup>101</sup> Franklin,<sup>102</sup> Allison<sup>103</sup> and Kay<sup>104</sup>. Although the technic of radical removal of esophageal cancer continues to improve, it is obvious that consideration must still be given to radiation therapy for this serious condition. Smithers and his associates<sup>105</sup> record the results of roentgen therapy in 44 patients with cancer of the esophagus. Thirty-two of the series had what was considered an adequate amount of therapy. Thirty of the entire group obtained some relief and 11 complete relief of symptoms. Three patients were still alive and free of symptoms at the end of six and one-fourth years, five years, and four and two-thirds years, respectively, after treatment.

Congenital atresia of the esophagus represents the most frequent type of congenital anomaly of this organ and consists of a blind upper esophageal segment and a lower segment communicating with the trachea. A series of instances of this anomaly are reported by Addey,<sup>106</sup> Chont and Starry<sup>107</sup> and Haight and

98 Schatzki, R., and Hawes, L. E. The Roentgenological Appearance of Extramucosal Tumors of the Esophagus, *Am J Roentgenol* **48** 1, 1942.

99 Dickes, R. R., Knudsen, A. F., and Franco, S. C. Multiple Polyps of the Esophagus. Report of a Case with Complicating Recurrent Gastrointestinal Hemorrhages, *Arch Int Med* **70** 121 (July) 1942.

100 Pennes, A. E. Leiomyosarcoma of the Esophagus, *Am J Roentgenol* **48** 336, 1942.

101 Brock, R. C. Cardio-Esophageal Resection for Tumor of the Cardia. Report of a Successful Case, *Brit J Surg* **30** 146, 1942.

102 Franklin, R. H. Two Cases of Successful Removal of the Thoracic Esophagus for Carcinoma, *Brit J Surg* **30** 141, 1942.

103 Allison, P. R. Report of Four Cases of Esophageal Carcinoma Treated by Excision, *Brit J Surg* **30** 132, 1942.

104 Kay, E. B. Experimental Observations on Reconstructive Intrathoracic Esophago-gastric Anastomosis Following Resection of the Esophagus for Carcinoma, *Surg, Gynec & Obst* **76** 300, 1943.

105 Smithers, D. W., Clarkson, J. R., and Strong, J. A. The Roentgen Treatment of Cancer of the Esophagus, *Am J Roentgenol* **49** 606, 1943.

106 Addey, W. A. A Case of Congenital Atresia of the Esophagus, *Brit J Radiol* **13** 179, 1940.

107 Chont, L. K., and Starry, L. J. Congenital Atresia of the Esophagus. Report of Four Cases, *Radiology* **40** 169, 1943.



Towsley<sup>108</sup> The last-mentioned report comments on the cases of 15 patients admitted to the University of Michigan Hospital during the past seven years. A detailed description of the first successful correction of the condition by operation is given. The authors note that since their paper was written 8 additional patients have been similarly treated, 4 of whom have been operated on successfully. The surgically ideal plan for the correction of this condition is a reconstruction of the continuity of the esophagus by an extrapleural ligation of the fistula and an end to end anastomosis of the esophageal segments. Another excellent example of modern surgical treatment is contained in a report by Davis and Stafford<sup>109</sup>. These authors describe the successful reconstruction of an extrathoracic esophagus in a child suffering from progressive esophageal stenosis secondary to the swallowing of concentrated lye, which finally resulted in complete obliteration of the esophagus from the neck to the stomach.

*Diaphragmatic Hernia*—The increasing frequency of recognition and diagnosis of diaphragmatic hernia is pointed out by Harrington<sup>110</sup> in an excellent article on the roentgenologic aspects of this condition. Between 1908 and 1925, this diagnosis was made in 30 instances, from 1926 to 1941, the condition was diagnosed more than 600 times, and the author has operated on 295 patients. This definite increase in frequency of recognition is due primarily to the development of roentgenologic methods of diagnosis. On the basis of his extensive experience, Harrington discusses the roentgenologic and clinical considerations in the diagnosis of this condition, taking up nontraumatic and traumatic hernia, esophageal hiatus hernia, congenital short esophagus, dilatation of the lower end of the esophagus with relaxation of the cardia of the stomach, and congenital diaphragmatic hernia due to structural deficiencies of the diaphragm. An interesting statement is that it was found that an average of three previous erroneous clinical diagnoses had been made before a correct diagnosis was established. Indications for surgical intervention are given.

Sahler and Hampton<sup>111</sup> stress the fact that the incidence of hiatus hernia lesions is considerably higher than has been appreciated, and they direct attention toward the frequent occurrence of hemorrhage. An exact description of the roentgen findings associated with this condition is given. They properly conclude that if neither gastritis nor ulceration is present in the hernial lesion bleeding will not be encountered.

An unusual symptom secondary to hiatus hernia is reported by Stubenbord<sup>112</sup>—namely, paroxysmal auricular fibrillation. Attacks of this arrhythmia were precipitated by overindulgence in alcohol or food or by worry and fatigue. Although the association of paroxysms of fibrillation with the hiatus hernia may have been only incidental, the report is of interest. A more unusual complication of diaphragmatic hernia is that reported by Deaner and his associates,<sup>113</sup> who present the

108 Haight, C, and Towsley, H. A. Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula. Extrapleural Ligation of Fistula and End-to-End Anastomosis of Esophageal Segments, *Surg., Gynec & Obst* **76** 672, 1943.

109 Davis, J. S., and Stafford, E. S. Successful Construction of an Extrathoracic Esophagus, *Bull. Johns Hopkins Hosp* **71** 191, 1942.

110 Harrington, S. W. Roentgenologic Considerations in the Diagnosis and Treatment of Diaphragmatic Hernia, *Am J Roentgenol* **49** 185, 1943.

111 Sahler, O. D., and Hampton, A. O. Bleeding in Hiatus Hernia, *Am J Roentgenol* **49** 433, 1943.

112 Stubenbord, W. D. Paroxysmal Auricular Fibrillation in Association with Hiatus Hernia. Report of a Case, *Ann Int Med* **18** 406, 1943.

113 Deaner, S., McMenemey, W. H., and Smith, S. M. Haemothorax Due to Strangulated Diaphragmatic Hernia, *Brit M J* **1** 72, 1943.

case of a 37 year old man who died two days after sudden onset of severe abdominal pain. The autopsy showed a hemothorax and, in addition, a loop of gangrenous stomach which had herniated through the diaphragm with a portion of the omentum.

*Gastritis*—The literature on gastritis continues to grow. Much of it is controversial, and for this reason the extraordinary observations of Wolf and Wolff,<sup>2</sup> already referred to, are extremely pertinent. These investigators studied a subject with a permanent gastric fistula, and a recent report deals with an investigation of changes in the appearance in the gastric mucosa in this person after various stimuli. Several experienced gastroscopists have expressed doubt as to whether the changes in color and the appearance of localized spots on the lining of the stomach represent disease or "gastritis," or whether they should be looked on as within the limits of normal. Wolf and Wolff considered that the small hemorrhagic lesions and so-called "pigment spots" regarded by many as signs of disease are in reality artefacts due to the trauma of the gastroscope itself or to the suction applied to the wall by the stomach tube in making the preliminary gastric analysis. They state that many of the signs of "gastritis" may be encountered in the normally functioning stomach or may be produced therein by minor traumas associated with instrumentation. In their patient the healthy gastric mucosa varied in appearance within a wide range. When the rate of production of acid by the parietal cells was relatively slow, the mucosa was always comparatively pale, and in this state it was relatively resistant to injury unless the continuity of its protective covering of mucus was interrupted. Accelerated production of acid and motor activity were always accompanied by hyperemia and mucosal engorgement. When vascular engorgement was prolonged, the rugae became intensely red, thick and turgid, presenting the picture of what has been called "hypertrophic gastritis." In this state the mucosa was unusually fragile, hemorrhages and small erosion resulting from even the most minor trauma. Lowering of the pain threshold occurred, and symptoms were often associated with this condition. Thus, the difference between hyperfunctioning of the stomach and "hypertrophic gastritis" was seen to be mainly one of degree. Continued exposure of a small erosion to the digestive action of gastric juice for four days resulted in a peptic ulcer. In this connection, reference has already been made to the observations of Wolf and Wolff on changes in gastroduodenal blood flow. As already noted, they observed that accelerations in blood flow in the mucosa of the stomach were associated with gastric motor activity, histamine stimulation and various psychologic stimuli.

The significance of hemorrhagic or pigment spots as observed by gastroscopy has received further consideration by Ruffin and Brown.<sup>114</sup> On the basis of a large number of control gastroscopies, with or without operation, these authors are in agreement with the conclusions already alluded to, that hemorrhagic or pigment spots in the gastric mucosa can be produced by aspiration of the stomach and may occur in healthy persons. They feel that such lesions probably have no clinical significance.

A study of 40 healthy volunteers by Fitzgibbon and Long<sup>115</sup> throws still further doubt on the wisdom of uncontrolled diagnoses of hypertrophic gastritis. Two of their 40 subjects showed definite hypertrophic changes although symptoms were completely absent. They make the obvious suggestion that a large series of normal

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<sup>114</sup> Ruffin, J. M., and Brown, I. W., Jr. The Significance of Hemorrhagic or Pigment Spots as Observed by Gastroscopy, *Am J Digest Dis* **10** 60, 1943.

<sup>115</sup> Fitzgibbon, J. H., and Long, G. B. A Gastroscopic Study of Healthy Individuals. A Preliminary Report, *Gastroenterology* **1** 67, 1943.

persons should be examined before one attempts to evaluate minor "hypertrophic" changes in the gastric mucosa

Hebbel<sup>116</sup> has attempted to correlate the occurrence of gastritis with the appearance of gastric and duodenal ulcer and gastric carcinoma by means of autopsy and surgical specimens. The control group of specimens consisted of stomachs examined at autopsy of 260 persons free of manifest gastric disease. Certain findings are of interest. Gastritis was rarely encountered below the age of 30, and the majority of the stomachs reexamined were free of any significant change. Atrophic changes appeared only twice in persons under the age of 50. One hundred and eight specimens were from patients over 50 years of age, and of these 30 per cent showed gastric atrophy. These findings lend credence to the view that "atrophic" gastritis is in part, at any rate, the result of an aging or degenerative process, and they suggest the obvious need for a gastroscopic study of a much greater number of normal persons in various age groups. Examination of surgical material from stomachs excised for ulcer or carcinoma supported the frequently reported constancy of gastritis associated with ulcer. The author feels that there is good evidence that the process is primary and not secondary to ulcer and must be separated from the processes leading to atrophy and achlorhydria, in which the body is regularly involved. Changes in the body mucosa were rare in the group with duodenal ulcer and common in the group with gastric ulcer. There was in the series no evidence that carcinoma of the stomach arises with unusual frequency at the site of already diffuse atrophic gastritis.

Maher and his associates<sup>117</sup> have reviewed their experiences based on gastroscopic and histologic examinations of 40 patients with peptic ulcer. On the basis of their observations they state that the gastritis associated with peptic ulcer is largely similar to that seen in patients with gastric cancer, a fact that strongly suggests that the gastritis per se may not be a specific precursor of either gastric cancer or peptic ulcer. They stress the frequent presence of microscopic evidence of atrophic gastritis in stomachs which appear normal gastroscopically as indicating the necessity for further study of control groups of stomachs.

The value of gastroscopy in the diagnosis of gastric tumor is thoroughly presented by Schindler and Letendre<sup>118</sup>. Among 95 cases of gastric tumor proved by operation, the lesion was not seen in 5 cases of gastric cancer, and in 5 others an incorrect gastroscopic interpretation was made. Sarcoma was mistaken for polyposis once, and a benign mucosal tumor was called malignant in 1 instance. In 3 cases, however, gastroscopic examination revealed a tumor not palpated or seen by the surgeon at laparotomy but found later in the resected specimens. There were 15 diagnostic failures on the first roentgen examination.

That clinical symptoms vary tremendously in patients showing chronic gastritis on gastroscopy is a fact receiving confirmation in various reports. Jackson and his associates<sup>119</sup> stress this fact in a review of over 1,000 gastroscopic studies. In 75 per cent of the patients pain was present, but as a rule there was no particular relationship to the ingestion of food and the duration of the pain was variable. Anorexia, indifference to food or fear of eating was noted in 45 per cent

116 Hebbel, R. Chronic Gastritis. Its Relation to Gastric and Duodenal Ulcer and to Gastric Carcinoma, *Am J Path* **19** 43, 1943.

117 Maher, M. M., Zinniger, M. M., Schiff, L., and Shapiro, N. Some Observations on Gastritis and Peptic Ulcer, *Am J M Sc* **205** 328, 1943.

118 Schindler, R., and Letendre, P. Analysis of Relationship of Surgery and Gastroscopy in Ninety-Five Cases of Gastric Tumor, *Surg, Gynec & Obst* **75** 547, 1942.

119 Jackson, C. L., Swalm, W. A., and Morrison, L. M. Diagnosis and Treatment of Chronic Gastritis, *Rev Gastroenterol* **9** 193, 1942.

of the patients, with loss of weight, weakness and nervousness in an important number. Nausea and vomiting were present in over one fifth of the patients, and constipation or diarrhea in 40 per cent. It would seem that the atypical and varying histories of patients with gastritis are in themselves a suggestive feature of this condition, but an accurate diagnosis cannot be based on the history alone. These authors advocate the obtaining of a biopsy specimen of gastric mucosa through an open tube gastroscope for an accurate evaluation of the underlying condition, and they claim satisfactory results by this method.

Hardt and his associates<sup>120</sup> examined gastroscopecally 119 patients with pulmonary tuberculosis with gastrointestinal symptoms. Atrophic changes in the gastric mucosa were noted frequently in far advanced pulmonary tuberculosis, and the authors state that the histopathologic picture indicates that these atrophic changes were primary, with secondary inflammatory changes. The comment of Ruffin in this connection is pertinent. He expressed the conviction that atrophy of the gastric mucosa in pulmonary tuberculosis is probably merely a local manifestation of a general condition, not primary gastritis at all but a degenerative process due to inadequate nutrition or actual vitamin deficiency. Flexner and Baum<sup>121</sup> also observed chronic superficial gastritis and gastric atrophy in an unusually large number of tuberculous patients. They could not correlate the abnormalities of the gastric mucosa, however, with the duration, severity or type of tuberculosis. Gastric symptoms failed to follow directly the gastroscopecally demonstrated lesions, and this was thought to be influenced by rest in bed, the reduction in food consumption caused by anorexia and the frequent presence of achlorhydria. Browne, McHardy and Wilen<sup>122</sup> made gastrosopic examinations of 50 tuberculous patients and found a normal mucosa in only one third of them. They state, however, that no gastritis of pathognomonic significance was established. In order to study further the problem of gastric symptoms in tuberculous patients, these investigators attempted to produce tuberculous lesions in the pyloric segment of the dog by local inoculation with living tubercle bacilli. The results indicated that the submucosal and hematogenous routes were the only successful methods of exciting a significant mucosal change. The authors hope to produce and endoscopically observe the development of mucosal changes of tuberculosis in animals for comparison with similar lesions in human beings.

A curious diffuse metaplastic gastritis in a patient with prolonged cachexia and macrocytic anemia is recorded by Sailer<sup>123</sup>. Diffuse areas of squamous metaplasia, regardless of the causative factors, have hitherto not been described in the gastric mucosa. He reports such changes proved by autopsy and diagnosed by gastroscopy as atrophic gastritis. No apparent cause for the gastric changes were found, but a deficiency of vitamin A was suggested as a possible etiologic factor.

Atrophy of the gastric mucosa was diagnosed positively in 10 of 11 cases of hypothyroidism and myxedema by Golding<sup>124</sup>. Such a finding is further evidence

120 Hardt, L. L., Weissman, M., and Coulter, J. S. Gastric Atrophy in Far Advanced Pulmonary Tuberculosis Complicated by Intestinal Tuberculosis, *Am J Digest Dis* **9** 404, 1942.

121 Flexner, J., and Baum, O. Gastrosopic Observations in Pulmonary Tuberculosis, *Am J M Sc* **204** 101, 1942.

122 Browne, D. C., McHardy, G., and Wilen, C. Gastric Mucosal Changes of Tuberculosis, *Am J Digest Dis* **9** 407, 1942.

123 Sailer, S. Diffuse Metaplastic Gastritis in a Patient with Prolonged Cachexia and Macrocytic Anemia, *Arch Path* **35** 730 (May) 1943.

124 Golding, F. C. The Association of Atrophic Gastritis with Hypothyroidism. A Preliminary Report of Eleven Cases, *Ann Int Med* **17** 828, 1942.

that gastric atrophy is frequently an expression of some form of deficiency disease, in this particular instance a deficiency of thyroid secretion or a nutritional deficiency secondary to the primary myxedema

Further studies on the gastric symptoms encountered in chronic alcoholism are presented by Gray<sup>125</sup> Gastroscopic examinations were made on 100 chronic alcoholic addicts taken at random, with ages varying from 24 to 66 These men had been drinking from 1 to 6 pints (0.5 to 3 liters) of alcoholic beverages daily for from three to fifty-two years The alcohol consumed included everything from wine to hair tonic Normal gastric mucosa was observed in 55 patients who had had an average daily alcohol consumption of 3 pints (1.5 liters) for more than twenty-one years Various forms of gastritis were noted in the remainder, 22 of whom showed superficial gastritis of varying degrees, 13 showed atrophy, and 8 showed a combination of superficial and atrophic gastritis Only 4 of the 55 patients with normal stomachs had subjective complaints, whereas 24 of the 45 patients with chronic gastritis presented definite symptoms

Schindler<sup>126</sup> states categorically on the basis of his wide experience that gastritis as a disease has a well established histopathologic picture, that it can be diagnosed reliably by gastroscopy and that therefore it can produce symptoms Few would disagree with this last statement, although there can be little doubt that innumerable patients showing marked changes in the gastric mucosa have few, if any, symptoms

As already suggested in some of the preceding papers, no characteristic clinical syndrome is typical of any form of gastritis Pollard and Cooper<sup>127</sup> studied 50 patients showing the characteristics of hypertrophic gastritis, they feel that the diagnosis can be made only by exclusion and by gastroscopy, and not on the basis of clinical symptoms Although admitting that gastritis can cause symptoms Tumen and Lieberthal<sup>128</sup> conclude that the presence of gastritis did not regularly influence the clinical course of duodenal ulcer in a carefully studied group of 50 patients with this disease Thirty-three of the patients with ulcer were shown by gastroscopy to have changes consistent with chronic gastritis These changes were variable in type, and 16 patients showed normal gastric mucosa, as far as could be determined A careful analysis of the patients' symptoms led to the conclusion that in individual cases it was possible that the gastritis might have added to the severity of the symptoms but that it often existed in an apparently symptomless manner It was impossible to postulate the presence or absence of associated gastritis on the basis of the nature of the symptoms or the character of the response to treatment An excellent clinical evaluation of chronic non-specific gastritis is to be found in a general article by Eustermann,<sup>129</sup> who states that simulation of the ulcer symptom complex or hemorrhage, or both, is a frequent manifestation of hypertrophic, erosive or ulcerative gastritis, on the other hand, that gastritis in its various forms is often symptomless He stresses the fact that chronic gastritis is generally refractory to treatment

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125 Gray, S. Epigastric Symptoms in Alcoholics With and Without Gastritis, *Gastroenterology* **1** 221, 1943

126 Schindler, R. On Chronic Epigastric Distress and Its Role in Chronic Gastritis An Analysis of the Problem, *Gastroenterology* **1** 44, 1943

127 Pollard, H. M., and Cooper, R. R. Is There a Clinical Syndrome Characteristic of Hypertrophic Gastritis? *J. Michigan M. Soc.* **41** 473, 1942

128 Tumen, H. J., and Lieberthal, M. M. The Significance of the Gastroscopic Findings in Patients with Duodenal Ulcer, *Gastroenterology* **1** 555, 1943

129 Eustermann, G. B. Chronic Nonspecific Gastritis Significance as a Clinical Entity, *Gastroenterology* **1** 54, 1943

Benedict<sup>130</sup> analyzes 117 cases of hypertrophic gastritis without other gastric or duodenal pathologic change. Two thirds of the patients were males, and the most frequent symptoms were pain and vomiting. No relationship was found between the severity of the pain and the activity of the gastritis as observed endoscopically. The relation of pain to the ingestion of food and its relief by food or alkali were variable, but the history and course were like those of ulcer in an important number of instances. Hemorrhage occurred in 49 cases, with hematemesis in 31. Although no specific treatment was effective, two thirds of the patients were definitely relieved by the use of a bland diet, belladonna, and alkali or hydrochloric acid. Benedict believes that clinical improvement in most cases was definitely correlated with improvement in the appearance of the gastric mucosa.

Hurst<sup>131</sup> comments on a specific cause of gastritis and hemorrhage, the use of acetylsalicylic acid. He makes the interesting statement that from his experience in hospital and private practice since 1939, he would expect to obtain a history of this drug as a direct cause of hemorrhage in at least one half of 58 cases in which chronic ulcer, cancer and cirrhosis could be excluded. He stresses the importance of administering acetylsalicylic acid immediately after meals in order to avoid gastric irritation. (The gastroscopic appearance of this type of irritation has been well described.) An interesting addition to the technic of gastroscopy is reported by Robinson<sup>132</sup>. Fluorescein was used topically on the mucous membrane of the stomach by instillation through a tube. Gastroscopy was then done in a series of cases. Four cases with positive findings are reported to demonstrate that this procedure was helpful in visualizing superficial ulcers of the stomach. The dye aids in outlining and demonstrating the ulcer, giving a more accurate estimate of the diameter of the ulceration.

Esophageal perforation during gastroscopy is rare. An unusual instance is reported by Paul and Lage<sup>133</sup>. Four hours after gastroscopy their patient complained of pain in the throat and difficulty in swallowing, and two hours later he had a chill with a rise in temperature. The patient died twenty-four hours after gastroscopy. At autopsy, no explanation could be found for the accident, and even when air was blown into the esophagus no perforation could be discovered. A fibrinous, acute, phlegmonous cellulitis with extreme edema was found in the upper part of the thorax, however, and a minute perforation must have occurred. The relatively slight danger associated with gastroscopy is indicated by the fact that Benedict<sup>134</sup> records only 3 perforations in 1,507 gastroscopies. In each instance the perforation was through the wall of the stomach, and death occurred only once.

*Experimental Ulcer*—Berk and his associates<sup>135</sup> have attempted to study in human beings and in animals the acidity of the ulcer-bearing area of the duodenum.

130 Benedict, E. B. Hypertrophic Gastritis. Gastroscopic and Clinical Studies, *Gastroenterology* **1** 62, 1943.

131 Hurst, A. Aspirin and Gastric Hemorrhage, *Brit. M. J.* **1** 768, 1943.

132 Robinson, H. M. Fluorescein—An Aid in Gastroscopy, *Am. J. Digest. Dis.* **10** 181, 1943.

133 Paul, W. D., and Lage, R. H. Perforation of Esophagus Caused by Flexible Gastro-scope. Report of Case with Autopsy, *J. A. M. A.* **122** 596 (June 26) 1943.

134 Benedict, E. B. Personal communication to the author.

135 Berk, J. E., Rehfuess, M. E., and Thomas, J. E. The Effect of Ulcer on Acidity and Neutralizing Ability in Duodenal Bulb, *Arch. Int. Med.* **70** 959 (Dec.) 1942, The Acidity of the "Ulcer-Bearing Area" of the Duodenum in Normal Persons, *Am. J. Digest. Dis.* **9** 276, 1942, Duodenal Bulb Acidity Under Fasting Conditions in Patients with Duodenal

The reaction of this portion of the duodenum has received scant attention. In normal subjects, these investigators found that the important ulcer-bearing first portion of the duodenum is an acid area, with an average  $pH$  in the fasting state of about 5.6 and after an Ewald meal of 5.0. Free acid is usually but not constantly absent. The duodenal bulb seems to be endowed with a capacity to neutralize, buffer and dilute the gastric chyme that generally exceeds the physiologic needs. None of the customary measures of gastric acidity in normal subjects can be used as a reliable index of the behavior of corresponding effective acidity ( $pH$ ) of the contents of the duodenal bulb. These authors conclude that in patients with duodenal ulcer, under fasting conditions the contents of the first part of the duodenum are more acid than in normal subjects with an average  $pH$  of 3.9. During fasting, free acid is found more often in the first part of the duodenum in these patients than in normal persons, free acidity when present tends to persist for longer periods. The ability of the duodenal bulb to neutralize buffer and dilute gastric secretions in patients with ulcer is impaired but not wholly lost. This is considered to be due to gastric hypersecretion and to a defective neutralizing capacity in the duodenal bulb as well. Fasting normal dogs display a greater neutralizing power in the duodenal bulb than do normal men, and the authors suggest that this may be due to the fact that dogs rarely, if ever, display a spontaneous duodenal ulcer.

The importance of acid in the genesis of ulcer receives additional confirmation in the experiments of Hay and his associates.<sup>136</sup> These investigators produced maximal secretion of hydrochloric acid from gastric pouches of dogs by embedding histamine in beeswax and injecting it intramuscularly to permit gradual liberation of the drug. With the employment of this agent, gastric and duodenal ulcers may be produced with some regularity in a number of laboratory animals. Their results are confirmatory of work previously reported by Varco.

Cheney<sup>137</sup> continues to report on gastric ulcers in chicks due to dietary deficiencies. Cinchophen gastric ulcers may also be produced in chicks but may be prevented or modified by a dietary factor. The fact that certain bile acids and salts prevent the development of deficiency ulcers in chicks and may have a similar action against experimental cinchophen ulcers the author explains by assuming that bile promotes the intestinal absorption of a fat-soluble ulcer-preventive factor, designated as vitamin U. He suggests that the ulcer-producing properties of cinchophen are due not to direct action on the lining of the stomach but to an indirect effect on the liver, which, in turn, may interfere with the elaboration and storage of the antiulcer factor and its delivery to the wall of the stomach. Some comparable explanation may be evoked in those cases of ulcer occasionally seen in connection with cirrhosis of the liver and mentioned in previous years by Ask-Upmark. Other possible dietary factors are suggested in the report by Sharpless,<sup>138</sup> in which he describes hyperplasia and ulceration of the forestomach epithelium in rats in association with a deficiency of cystine, riboflavin, pyridoxine or choline. Sodium taurocholate or pepsin and hydrochloric acid increased the incidence of lesions in animals fed the poor diets. In

Ulcer, Arch Surg **45** 405 (Sept) 1942, Duodenal Bulb ("Ulcer Bearing Area") Acidity in Fasting Normal People, J Clin & Lab Med **27** 1501, 1942.

136 Hay, L. J., Varco, R. L., Code, C. F., and Wangenstein, O. H. Experimental Production of Gastric and Duodenal Ulcers in Laboratory Animals by the Intramuscular Injection of Histamine in Beeswax, Surg, Gynec & Obst **75** 170, 1942.

137 Cheney, G. Cinchophen Gastric Ulcers in Chicks, Arch Int Med **70** 532 (Oct) 1942.

138 Sharpless, G. R. Diet and Epithelial Hyperplasia in the Forestomach of Rats and Mice, Cancer Research **3** 108, 1943.



experiments on rats, Zucker and Berg<sup>139</sup> noted that diets adequate for excellent growth in all respects will lead to a high incidence of predominantly antral lesions if calcium is omitted from the salt mixture. Vitamin D deficiency plays no role.

Experimental acute gastric ulcers were produced in mice and in guinea pigs by Weedon<sup>140</sup> by exposure to sulfur dioxide gas. With minor concentrations of the gas only gastric distention was noted, but when the concentration was increased distention occurred at an earlier date and multiple hemorrhagic ulcers with perforations were frequent.

Protection against experimental ulcers has been obtained by various procedures. The survival time of dogs in which histamine was used to produce peptic ulcers was increased by Shock and Fogelson<sup>141</sup> by daily feeding of 0.5 Gm of a fatty alcohol sulfate (Dreft). This denaturant inactivated the pepsin of the gastric juice and thus decreased its digestive powers. The application of this principle to human beings has not yet been proved of practical value.

Hands and his collaborators<sup>142</sup> have previously reported that enterogastrone depresses the motor and secretory activity of the stomach, and in an effort to determine its effect on Mann-Williamson ulcers they treated a series of 25 such ulcers in dogs. Control animals treated intravenously with an extract of pork muscle died of jejunal ulcer in four to thirty weeks, the average postoperative survival time being just under sixteen weeks. The muscle extract did not inhibit gastric secretion or motility. Of the dogs given injections of enterogastrone, jejunal ulcers developed in only 6. Eight of the 25 animals died within nine months without ulcer, living an average of nineteen weeks following operation. Eleven dogs were still alive without ulcer for more than nine months, and 7 of these for more than one year. Five of the latter 7 had been without treatment for from four to five months without ulcer developing. The authors are of the opinion that enterogastrone extract, even though as yet impure, has a remarkable potency in preventing jejunal ulcer in Mann-Williamson dogs. Analogous experiments were carried out by Beaver and his collaborators<sup>143</sup> on standard Mann-Williamson dogs. In all, 142 animals were employed, of which 42 were treated with an extract of urine of pregnant women, 42 with an extract of urine of normal women, and 30 with an extract of urine of patients having active symptoms of duodenal ulcer. The untreated dogs died within an average of seventy-one days. Of those treated with the extract of urine of pregnant women, 85 per cent of the animals were benefited. Of those treated with the extract of urine of normal women, 62 per cent were benefited. Only 24 per cent of the 30 dogs treated with the urine of patients with ulcer were benefited. Experimental results with extracts of urine of normal men are not complete, but the authors believe that the urine of normal men contains much less of the protective substance than the urine of normal women, though more than the urine of patients having active symptoms of ulcer. They believe that this protective substance is closely related to the gonadotropic hormone found

139 Zucker, T. F., and Berg, B. N. Calcium Deficiency and Gastric Lesions in the Rat, *Proc. Soc. Exper. Biol. & Med.* **53**: 34, 1943.

140 Weedon, F. R. Experimental Acute Gastric Ulcer Produced in Animals by Exposure to Sulfur Dioxide Gas, *New York State J. Med.* **42**: 620, 1942.

141 Shock, D., and Fogelson, S. J. The Effect of a Protein Denaturant on Histamine Ulcers, *Quart. Bull., Northwestern Univ. M. School* **16**: 142, 1942.

142 Hands, A. P., Greengard, H., Preston, F. W., Fauley, G. B., and Ivy, A. C. Prevention of Experimental Gastrojejunal Ulcer by Enterogastrone Therapy, *Endocrinology* **30**: 905, 1942.

143 Beaver, D. C., Sandweiss, D. J., Saltzstein, H. C., Farbman, A. A., and Sanders, A. W. The Effect of Urine Extracts on the Prevention and Healing of Experimental Ulcers in Dogs, *Am. J. Clin. Path.* **12**: 617, 1942.



in the urine of pregnant women and that its effect is not due to inhibition of gastric secretion or acid in the Mann-Williamson ulcers. Microscopically, the beneficial effect is shown by fibroblastic proliferation, new formation of blood vessels and epithelization of the mucosa.

Friedman and Podolsky<sup>144</sup> investigated the possibility that tissue proliferation at the site of experimental ulcers in urine-treated animals might be due to anterior pituitary substance with high prolactin activity. Experiments were carried out in pigeons, and on the fifth day after injection the crops were examined for increase in weight and for proliferation of the crop glands as suggested by McShan and Turner in 1937. Extracts of urine from pregnant and from nonpregnant women were used. None of the treated birds showed a gain in crop weight although unmistakable evidences of crop proliferation were found in 1 bird of the control series and in none of the urine-treated series. The conclusion was reached that urine extracts which can cause fibroblastic proliferation and epithelization of the experimental ulcer do not do so because of prolactin. The results were suggestive but not conclusive, inasmuch as the extract employed did not have a high content of prolactin.

*Clinical Ulcer*—Demonstration of gastric ulcerations in cases of diaphragmatic hernia is not too common. Rude<sup>145</sup> describes the clinical aspects of the condition and gives in detail important roentgenologic findings. The condition is best demonstrated with the patient recumbent in the Trendelenburg position with the body turned on the left side. Huber and Andreson<sup>146</sup> report a small series of interesting cases in which a gastric or duodenal ulcer was associated with similar lesions in the lower end of the esophagus or in the cardia. Ulcerations were demonstrated in cases of hiatus hernia, esophageal diverticulum and mega-esophagus.

An uncommon site of primary ulceration is the jejunum. Dowdle<sup>147</sup> reports the case of a patient with chronic dilatation of the duodenum produced by obstructive, multiple jejunal ulcers. Nine additional cases have appeared in the literature, and in most instances the ulcers were found in the proximal portion of the jejunum opposite the mesenteric attachment.

The occurrence of recent acute peptic ulcer in the sixth and later decades of life is not particularly uncommon, but the report of Meyer and Saphir<sup>148</sup> is of some interest. Sixteen patients are reported on, the youngest being 60 years of age and the oldest 83. A clinical diagnosis was made for 5 patients. The fact that for the 11 other patients the diagnosis was not correctly made may have been due in part to the fact that an atypical history was obtained. This is particularly likely to occur with patients of this age group, in whom the threshold of pain perception is distinctly higher than in younger persons. As was to have been expected, microscopic changes in the region of the ulcer showed arterial changes that were definitely more severe than those noted in younger patients. Surgical operation on such patients, performed for perforation or because of the possibility

144 Friedman, M. H. F., and Podolsky, H. M. Prolactin and Healing of Experimental Peptic Ulcer, *Endocrinology* **31** 689, 1942.

145 Rude, J. C. Healed Gastric Ulcer with Associated Inflammatory Fibrotic Changes in a Diaphragmatic Hernia, *Radiology* **38** 729, 1942.

146 Huber, F., and Andreson, L. H. Gastric and Duodenal Ulcer Associated with Lesions of the Lower End of the Esophagus and the Cardia of the Stomach, *Am J Roentgenol* **48** 158, 1942.

147 Dowdle, E. Multiple Primary Nonspecific Jejunal Ulcers with Chronic Duodenal Dilatation, *Ann Surg* **116** 348, 1942.

148 Meyer, J., and Saphir, O. Peptic Ulcer in the Aged. A Clinical and Postmortem Study, *Am J Digest Dis* **10** 28, 1943.

of carcinoma, is not contraindicated because of age alone. A case of ulcer in a person of extreme age is reported by Tanner<sup>149</sup>. This patient died of perforation of a duodenal ulcer at the age of 91. Histologic examination showed a typical chronic duodenal ulcer.

That vascular changes may frequently complicate the problem of ulcer is indicated in an article by Schenken and his associates<sup>150</sup>. The average patient with ulcer, even in the later decades of life, has a relatively low blood pressure. These authors, in a review of the postmortem examinations of patients with gastric or duodenal ulcer, were impressed by the high incidence of hypertension and pancreatic erosion in those patients who died of massive hemorrhage. Of a group of patients who died of hemorrhage, nearly 60 per cent had hypertension and 75 per cent of the group had either hypertension or erosion of the pancreas or both. These findings indicate the cause of the increased mortality from hemorrhage in older patients with ulcer.

Variations in the percentage incidence of gastric and of duodenal ulcer continue to appear in various parts of the world. A recent report from Australia by Cleland,<sup>151</sup> based on postmortem examinations, shows that of 207 active or healed ulcers 60 per cent were gastric. There had been no change in the relative incidence of gastric and duodenal ulcers over a period of twenty-two years. In persons less than 50 years of age the incidence of gastric and that of duodenal ulcers were about equal, after that age there was a rapid increase in the incidence of gastric over duodenal ulcers.

The infrequency with which ulcer occurs in Southern Negroes has been mentioned on numerous occasions, and an article by Finney<sup>152</sup> again stresses this point in an analysis of cases of ulcer in Alabama. Whether the incidence in Negroes will increase under war conditions and with increased industrialization of the South will be a matter for interesting speculation. A report from southwest India by Somervell<sup>153</sup> covers his experience with 4,000 patients operated on during the past twenty years. In a former paper he pointed out that peptic ulcer in this part of India seemed chiefly due to deficient diet, the greatest deficiency possibly being that of vitamin A. In the present report he states that an extensive study of the vitamin situation in southwestern India showed that vitamins A and B<sub>2</sub> are noticeably lacking and, in addition, that there is an overwhelming preponderance of carbohydrates in the diets, with relatively little protein and fat, a condition which appears to increase gastric acidity. He destroys one of the time-honored colonial traditions in stating that the eating of curry has little to do with ulcer, since in parts of India where ulcer is relatively uncommon, even hotter curry is eaten than in other parts of the country. One point that may be questioned in his report is the statement that rapid reduction of gastric acidity is obtained by the ligation of a sufficient number of arteries in the wall of the stomach, in view of recent experimental evidence, such a statement can hardly be convincing.

The relatively high incidence (approximately 10 per cent) of peptic ulcer in association with polycythemia has been known since 1905. Statistically, the

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149 Tanner, N. C. Gastroduodenal Surgery in the Aged, *Brit. M. J.* 1:563, 1943.

150 Schenken, J. R., Burns, E. E., and Maes, U. The Role of Hypertension and Pancreatic Erosion in Massive Hemorrhage from Gastric and Duodenal Ulcers, *Surg., Gynec. & Obst.* 74:1058, 1942.

151 Cleland, J. B. Gastric and Duodenal Ulcers in South Australia, *M. J. Australia* 2:295, 1942.

152 Finney, J. O. Peptic Ulcer. An Analysis of One Hundred and Eighty-Eight Cases with Special Reference to Hemorrhage, *J. M. A. Alabama* 12:73, 1942.

153 Somervell, T. H. Further Contributions to the Causation and Treatment of Duodenal Ulcer and Its Complications, *Brit. J. Surg.* 30:113, 1942.

record of 163 cases of polycythemia vera by Tinney and his associates<sup>151</sup> is of interest. Eleven of the patients were definitely shown to have ulcer, and 5 others gave a typical history and had had a diagnosis of ulcer made elsewhere but the presence of ulcer could not be proved at the time of examination. Such ulcers, in all probability, are the result of thromboses in small gastric or duodenal vessels.

Reports of verified Cushing ulcers are not too frequent. Whigham<sup>155</sup> reports one such ulcer in a young woman who suffered severe extensive cutaneous burns. An autopsy performed eleven days after the accident revealed a large acute ulcer in the first portion of the duodenum. There was nothing in the past history to suggest a previous ulceration. In this regard it is of some interest to mention the observations made on patients who were badly burned in the Coconut Grove fire in Boston.<sup>156</sup> Among those patients admitted to the Massachusetts General Hospital no symptoms of ulcer were noted, but over half of the patients had occult blood in the stools. Autopsy in 3 cases showed extensive submucosal hemorrhage in the duodenum in 1 instance and duodenal and gastric lesions of a petechial nature in the other 2.

Traumatic gastroduodenal ulcers are rare but probably occur. Veidlan<sup>157</sup> is responsible for the statement that in only 1 of 4 cases is ulcer recognized as such during life. This frequent, though unrecognized, occurrence, together with the high frequency of accidents in these days, introduces a considerable possibility of error in any conclusion as regards traumatic ulcer. Although the traumatic origin of this disease has never been clearly demonstrated, it is nevertheless possible to regard trauma as a determining cause of a chronic gastric lesion if no dyspeptic symptoms existed prior to the accident, provided that the trauma was of sufficient violence involved the epigastrium and was followed by immediate objective symptoms. Case histories illustrate the possible etiologic importance for chronic gastric lesions of cerebral trauma, cutaneous burns, septicemia and lead poisoning. The discussion is of interest chiefly from a medicolegal point of view. Traumatic perforation of a gastric ulcer is obviously less difficult to understand than the conditions just alluded to, but such a finding is still not too common. Gallo and Pozzo<sup>158</sup> report traumatic perforation of a gastric ulcer following a kick in the epigastrium by a horse. A dense, firm ulcer was discovered at operation, although no history of preexisting symptoms of ulcer could be elicited. The literature is reviewed and several cases abstracted.

A fascinating study by Horton<sup>159</sup> concerns the production of acute duodenal ulcer in cases of cephalgia due to histamine. This condition, which has only recently been recognized, invariably presents the story of acute attacks of excruciating pain involving the eye, temple and neck and often the face. These attacks have been refractory to other types of treatment but have been eradicated within two to three weeks by "desensitization" to histamine. Ten such cases are presented by the author, in which there was a direct relationship between an acute

154 Tinney, W. S., Hall, B. E., and Giffin, H. Z. Polycythemia Vera and Peptic Ulcer, Proc. Staff Meet., Mayo Clin. **18** 24, 1943.

155 Whigham, J. R. M. Severe Burns Associated with Duodenal Ulceration, Brit. J. Surg. **30** 178, 1942.

156 Mallory, T. B., and Brickley, W. J. Management of the Coconut Grove Burns at the Massachusetts Hospital. Pathology, with Special Reference to the Pulmonary Lesions, Ann. Surg. **117** 865 (June) 1943.

157 Verdan, C. Gastro-Duodenal Ulcers as a Result of Accidents, Gastroenterologia **67** 1, 1942.

158 Gallo, A. G., and Pozzo, J. J. Traumatic Perforation of a Gastric Ulcer. Semana med. **2** 133, 1942.

159 Horton, B. T. Histaminic Cephalgia Resulting in Production of Acute Duodenal Ulcer, J. A. M. A. **122** 59 (May 1) 1943.

duodenal ulcer with a crater and histamine cephalgia. The formation of the ulcer in each instance was secondary to the attacks of intractable headache. During the attacks the gastric acid rose to an abnormally high level, just as would have been the case if the patient had received approximately 0.35 mg of histamine subcutaneously. The subjects were all hypersensitive to histamine, to such a degree that even 0.01 mg of histamine had been sufficient in many instances to precipitate a rise in gastric acidity. Treatment by means of desensitization to histamine, without other treatment for the duodenal ulcer itself, not only caused cessation of the headaches but permitted the duodenal ulcer to heal properly, within two weeks.

Synchronous studies of gastroduodenal motility with tandem balloons have been made by Patterson and Sandweiss,<sup>160</sup> with particular reference to the relationship between gastroduodenal motility and symptoms associated with duodenal ulcer in the human. Distress from ulcer occurred only when the stomach and duodenum were simultaneously exhibiting motility or when the duodenum alone was showing motor activity. It did not occur when the duodenum was in a quiescent phase. In other words, the studies indicate that the duodenum must be in an active motor phase for the patient with duodenal ulcer to experience pain. As the authors point out, however, these findings do not necessarily indicate that duodenal motility is the only factor responsible for the distress associated with ulcer. In keeping with other investigative reports, these authors found that the duodenum sometimes has its periods of motor activity long before the stomach does, which indicates that the duodenum acts independently of the stomach.

A curious picture of pain like that of duodenal ulcer without the existence of an ulcer is reported by Yenikomshian and Shehadi.<sup>161</sup> Gastrointestinal disturbances caused by hookworm disease may appear in different clinical forms, including that of duodenal ulcer. Estimation of free gastric acid shows a rise to a level higher than that obtained in the average case of duodenal ulcer, in spite of varying degrees of severe anemia. Roentgenologic studies in these cases of ankylostomiasis show evidence of swelling of the duodenal mucosa, inconstant deformity of the duodenal bulb, hyperperistalsis of the stomach and duodenum, and usually reversed peristalsis of the duodenum without obstruction. Administration of a vermifuge results in the elimination of epigastric pain within twenty-four hours and restoration of the contour of the duodenal wall in from eleven to twenty-four days.

Articles on perforated ulcer are numerous. Of these, only a few have been taken for review. One by Harrison and Cooper<sup>162</sup> presents a detailed analysis of 57 cases of acute perforated peptic ulcer. The study was undertaken in order to test the validity of the widespread opinion that if a peptic ulcer perforates and the patient recovers after closure, subsequent permanent healing of the ulcer is to be expected. Of 41 patients surviving perforation, less than one fifth remained well, 25 had an asymptomatic period immediately following operation, averaging one and eight-tenths years, 7 patients had continuous symptoms. The patient reporting the longest asymptomatic period had this period abruptly terminated by a second perforation. The authors conclude that after closure of a perforated

160 Patterson, T. L., and Sandweiss, D. J. The Relationship Between Gastro-Duodenal Motility Phases and Symptoms Associated with Duodenal Ulcer in the Human, *Am J Digest Dis* 9 375, 1942.

161 Yenikomshian, H. A., and Shehadi, W. H. Duodenal Ulcer Syndrome Caused by Ankylostomiasis. Report of Twenty-Five Cases with Gastric Acidity and Roentgenologic Studies, *Am J Roentgenol* 49 39, 1943.

162 Harrison, C., and Cooper, F. W., Jr. Immediate and Late Results of Perforation of Peptic Ulcer, *Ann Surg* 116 194, 1942.

ulcer every patient should have his case evaluated anew and be treated as any other patient with ulcer. A slightly more optimistic report is that of Barber and Madden,<sup>163</sup> who carried out a follow-up study on a small group of 21 patients with perforated ulcers. Two thirds of these were considered to be free of symptoms of ulcer but such a finding is not in accord with the usual clinical experience.

Activity of peptic ulcer during pregnancy is rare, and complications are still more uncommon. For this reason, the discussion by Sandweiss and his collaborators<sup>164</sup> on deaths from perforation of gastroduodenal ulcer during pregnancy and puerperium is of interest. One such case is reported, and the literature is completely reviewed. In all, 14 cases have been reported, and the point is made that for pregnant women who have a previous history suggestive of ulcer medical management should be immediately instituted if epigastric symptoms occur during the second or third trimester of pregnancy. Another rare complication is that reported by Heathfield<sup>165</sup> who records the death of a patient from a solitary abscess of the liver secondary to a perforated duodenal ulcer.

Ulfelder and Allen<sup>166</sup> have made an analysis of 334 cases of patients with acute perforation of a gastric or duodenal ulcer, seen between 1916 and 1940. The mortality by five year periods showed no significant change during the past fifteen years. During the winter months the mortality was appreciably higher than during other seasons, and there appeared to be some relation between this mortality and the virulence of recurrent infections of the respiratory tract. As was to have been expected, the mortality rose with the patient's age. In agreement with all experienced surgeons, they noted that the interval between perforation and closure is of fundamental prognostic importance. An interesting fact is the observation that in the majority of patients who recovered when more than fifteen hours had elapsed between the onset and operation, the perforation had already spontaneously healed.

Sanders<sup>167</sup> reports an unusual combination of perforated peptic ulcer and acute appendicitis. Nine other such cases have been reported. The preoperative diagnosis in all the cases reviewed was acute appendicitis, with or without perforation, and only postoperatively was the existence of the two lesions found. The wisdom of the long-established rule to operate whenever the diagnosis of appendicitis is made is reaffirmed.

Allusion has already been made to a possible new procedure in surgical treatment for ulcer—namely, insertion of jejunal transplants in the gastric wall. Andrus, Lord and Stefko<sup>168</sup> have shown in animals that gastroenterostomy alone failed to prevent a marked diminution in the average  $p_H$  of the mucosa of seven

163 Barber, R. F., and Madden, J. L. Acute Gastroduodenal Perforation, *Am J Surg* 59 484, 1943

164 Sandweiss, D. J., Podolsky, H. M., Saltzstein, H. C., and Farbman, A. A. Deaths from Perforation and Hemorrhage of Gastroduodenal Ulcer During Pregnancy and Puerperium. A Review of the Literature and Report of One Case, *Am J Obst & Gynec* 45 131, 1943

165 Heathfield, K. W. G. Liver Abscess Following Perforated Duodenal Ulcer, *Lancet* 2 155, 1942

166 Ulfelder, H., and Allen, A. W. Acute Perforation of Ulcers of the Stomach and Duodenum, *New England J Med* 227 780, 1942

167 Sanders, A. W. Perforated Peptic Ulcer Complicated by Acute Purulent Appendicitis. Case Report, *Am J Surg* 57 364, 1942

168 Andrus, W. deW., Lord, J. W., Jr., and Stefko, P. Comparative Effects of Gastroenterostomy and Pedicle Jejunal Graft on the  $p_H$  of the Gastric Mucosa, *Proc Soc Exper Biol & Med* 52 99, 1943. Lord, J. W., Jr., Andrus, W. deW., and Stefko, P. Effects of Jejunal Transplants on the Experimental Production of Peptic Ulcers, *Arch Surg* 46 459 (April) 1943

different regions of the stomach following injection of histamine. After conversion of the gastroenterostomy to a jejunal graft, however, the normal response to histamine was reversed in all 6 dogs. After these experiments the effects of such jejunal transplants were studied on the experimental production of peptic ulcers of the duodenum through daily intramuscular injection of a mixture of histamine phosphate and beeswax in liquid petrolatum, as reported by Varco and his associates (1941). In the single animal in which it could be satisfactorily carried out, implantation of a pedicle graft of jejunum into the stomach was followed by healing of the duodenal lesions despite continuation of the injections of histamine. The results also suggest the efficacy of such transplants in preventing the development of duodenal erosion and ulceration during continued exposure to histamine.

The adequacy of most statistical methods for evaluating the results in the treatment for peptic ulcer is severely criticized by Hollander and Mage<sup>169</sup>. These authors give an excellent discussion of this phase of the problem of ulcer and present a statistical procedure of their own which appears to be satisfactory. On the basis of such statistical studies, they analyze the surgical results in patients with duodenal ulcer who were subjected to subtotal gastrectomy during the years 1923 to 1934. In this group, the average total incidence of recurrence was about 9 per cent, a much higher figure than that which is usually considered. A careful perusal of the points made by these authors is recommended to those who are interested in carrying out statistical studies. Mage<sup>170</sup> subsequently carried out a statistical analysis of the cases of 600 patients with ulcer on whom subtotal gastrectomies had been performed in the last seventeen years. In 502 patients with duodenal ulcer and 98 with gastric ulcer thus treated, there were 41 recurrences (all but 1 taking place in patients with duodenal ulcer), or approximately a 7 per cent incidence of recurrence. Recurrence of ulcer was not noted before the expiration of a year postoperatively, and in the majority of cases it was found in the first four years following operation. One recurrence, however, was recorded after twelve years of freedom from symptoms. Of the entire group of resected specimens, 30 contained the ulcer, hence removal of the ulcer at operation is not a *sine qua non* for insuring success of subtotal gastrectomy. No ulcers occurred in patients without free hydrochloric acid in the gastric secretion. Subtotal resection created achlorhydria in at least 90 per cent of patients with gastric ulcer and in about 50 per cent of those with duodenal ulcer. A final conclusion, with which the reviewer is in entire sympathy, is that "Radical resection is considered to be the best available operation for duodenal ulcer, but the present impression is that it leaves much to be desired."

The mortality subsequent to subtotal gastric resection for ulcer is relatively low. Miller<sup>171</sup> gives a mortality of 2.8 per cent in his entire group of 230 cases in which the operation was done. This group comprised instances of all types of ulcer, including those complicated by gross and massive hemorrhage. Lahey and Marshall<sup>172</sup> cite a similar mortality of 2.7 per cent for all gastric, duodenal, and gastrojejunal ulcers, exclusive of gastrojejunal fistulas. A mortality of 3.2 per cent is reported by them for 251 subtotal resections for ulcers of all types,

169 Hollander, F, and Mage, S. A Statistical Method for Evaluating the Results of Treatment for Peptic Ulcer, *Surg, Gynec & Obst* **76** 533, 1943.

170 Mage, S. Recurrence of Ulceration Following Subtotal Gastrectomy in the Treatment of Gastroduodenal Ulcer, *Ann Surg* **116** 729, 1942.

171 Miller, G. G. Report of Two Hundred and Thirty Cases of Subtotal Gastric Resection for Peptic Ulcer, *Surgery* **12** 383, 1942.

172 Lahey, F. H., and Marshall, S. F. Surgical Management of Some of the More Complicated Problems of Peptic Ulcer, *Surg, Gynec & Obst* **76** 641, 1943.

and a 4.4 per cent rate for 46 consecutive subtotal resections performed solely for gastrojejunal ulcers. These authors rightly stress the wisdom of such radical surgical treatment as the only successful means of handling the particular problem of gastrojejunal ulcer. Experience seems to be unanimous that medical measures are not effective in preventing chronic invalidism for patients with this condition. Delgado<sup>173</sup> cites an even lower mortality following gastrectomies on more than 500 patients with ulcer. This author claims that only 2 per cent of patients failed to survive the operation, and he mentions only 1 recurrent ulcer. In view of Hollander's remarks on a collection of statistics of late surgical results, it is pertinent to point out that of a group of 500 patients only 75 were followed, therefore, the statistical value of this particular communication is invalidated.

Subtotal gastrectomy is far from a physiologic procedure, and it is true that many patients subjected to this form of operation are far from free of symptoms in spite of the fact that specific symptoms of ulcer may be lacking. Freeman and his collaborators<sup>174</sup> attempted a detailed study to determine the effect of complete removal of the stomach from growing monkeys. Five of the 6 gastrectomized animals died within one hundred and twenty-eight to one hundred and fifty-two days following gastrectomy. Death was always preceded by anorexia, lassitude, diarrhea and dehydration, and in 1 instance there was presence of gross blood in the stools. One animal survived for a year and a half but failed to gain weight. The animal that lived the longest differed from its control as follows: The emptying time of the upper part of the small intestine was increased, the animal failed to gain weight, the serum phosphatase was increased, the serum calcium was decreased, the parathyroid gland was enlarged and contained large cells with vacuolated cytoplasm, the stools were intermittently watery and foul smelling, there was a diminution in the size of the skeleton.

Evensen<sup>175</sup> studied alimentary hypoglycemia in 38 patients who had been subjected to gastroenterostomies and in 95 who had had subtotal gastrectomies. Of 100 control subjects, 7 per cent described hypoglycemic symptoms during dextrose tolerance tests. Thirty per cent of those patients with gastroenterostomies had similar symptoms after dextrose tolerance tests, and 15 per cent of the group of patients on whom subtotal gastrectomies had been performed. Evensen's investigations also revealed that the performance of any work after meals may be a contributing factor to the production of hypoglycemic symptoms in patients after operations on the stomach.

The effect of subtotal gastric resection on gastric acidity was studied by Friedell, Shaar and Walters<sup>176</sup>. These authors obtained a reduction of gastric acidity in 75 per cent of the cases of duodenal ulcer for which this operation was performed and a relative achlorhydria in all of the cases of gastric ulcer. Histamine stimulation in many of the relatively achlorhydric patients still produces secretion of free acid. The optimal amount of stomach to be removed would seem to be somewhere between one half and two thirds, according to Holman and McSwain<sup>177</sup>. Their

173 Delgado, R. The Life of the Gastrectomy Patient. Results of Gastrectomy for Gastric and Duodenal Ulcer, *Arch argent de enferm d ap digest y de la nutricion* **17** 590, 1942.

174 Freeman, S., Hough, V. H., Wigodsky, H., and Ivy, A. C. The Effect of Gastrectomy upon Growing Monkeys, *Gastroenterology* **1** 199, 1943.

175 Evensen, O. K. *Acta med Scandinav*, 1942, supp 126, cited in *Alimentary Hypoglycaemia After Stomach Operations*, editorial, *Lancet* **2** 626, 1942.

176 Friedell, M. T., Shaar, C. M., and Walters, W. Effect of Gastric Resection on Gastric Acidity, *J. A. M. A.* **120** 666 (Oct 31) 1942.

177 Holman, C. W., and McSwain, B. Gastric Acidity Following Gastric Resection, *Surgery* **13** 916, 1943.



postoperative results seem to indicate that removal of more than two thirds of the stomach does not increase to any important degree the number of patients with reduced acidity or anacidity

In an attempt to evaluate surgical procedures Hinton<sup>178</sup> discusses the intractable duodenal ulcer and expresses the opinion that the only true indication of intractability in cases of duodenal ulcer is constant pain. He does not agree that pyloric stenosis as such is an indication for surgical intervention, and he feels that a stenosing or obstructing ulcer not accompanied by pain does not require surgical intervention. Such a statement seems overconservative and to require a definition of the term stenosis. It is not infrequent to have a degree of pyloric stenosis sufficient to interfere with normal nutrition and still have no symptoms of active ulcer. In these cases, it certainly would seem the part of wisdom to relieve the situation by an adequate surgical procedure. Another statement that seems to require comment is that patients who will not cooperate under medical management should not be operated on. Such an attitude hardly seems justifiable, inasmuch as there are many instances in which complete and adequate cooperation is impossible because of economic or social reasons, and in many of these cases an adequate surgical operation again is effective although at times the results are much less satisfactory than in patients who fully understand their condition and the requirements of medical treatment. In a report by Collins and Ward<sup>179</sup> overconservatism against reasonable surgical intervention again seems to be apparent. These authors review their experience with 29 jejunal ulcers, all postoperative. They conclude that for the uncomplicated postoperative jejunal ulcer adequate medical treatment persistently carried out until healing is assured, with careful control of the patient's regimen for an indefinite period afterward, constitutes the safest plan of treatment. This does not coincide with the conviction of most doctors who are conversant with the problem of ulcer. In most persons with postoperative jejunal ulcer recurrences are frequent and complications not uncommon. Modern gastric operations when performed by adequately trained surgeons can be done with a minimum of risk and a maximum of postoperative health for this distressing postoperative complication. Even under the best conditions of medical regimen few patients suffering from this type of ulcer fail to have recurrences.

One of the complications of gastroenterostomy is reported by Smith and Rivers,<sup>180</sup> namely, gastroileal ulcer. These authors report 9 cases of gastroileostomy, an important but fortunately rare surgical error. Gastroileitis was present in 1 of these cases and gastroileal ulcer in 3. The symptoms, as should be expected, were entirely similar to those of gastrojejunal ulcer.

The occasional indication for jejunal alimentation in the surgical management of peptic ulcer is discussed by Colp and Druckerman.<sup>181</sup> Jejunostomy for alimentation was performed in a series of 51 patients suffering from recurrent peptic ulcer. It was used as a preliminary, palliative, complementary and supplementary measure in the surgical treatment of peptic ulcer. The indications for and clinical applications of this maneuver are fully described. Such a procedure

178 Hinton, J. W. The Intractable Duodenal Ulcer. Evaluation of Surgical Procedures, *Ann Surg* **117** 498, 1943.

179 Collins, E. N., and Ward, G. J. Current Trends in the Treatment of Jejunal Ulcer, *Cleveland Clin Quart* **9** 159, 1942.

180 Smith, L. A., and Rivers, A. B. Gastroileostomy and Gastroileal Ulcer, *Surg, Gynec & Obst* **76** 110, 1943.

181 Colp, R., and Druckerman, L. J. The Indications for Jejunal Alimentation in the Surgery of Peptic Ulcer, *Ann Surg* **117** 387, 1943.



is not commonly used but for badly depleted patients may offer an effective way of shortening convalescence and of avoiding serious postoperation depletion.

Although not limited to the results of surgical treatment of ulcer, the problem of intestinal distention complicating abdominal operation is an important one. In a large percentage of cases, gaseous distention of the intestine is due to swallowed air. Proof of this is mentioned in an article by Singleton, Rogers and Houston,<sup>182</sup> who note that patients with excision of the esophagus or with a complete stricture and gastrostomy feeding rarely have appreciable amounts of gas in the bowel. The measures that are needed to combat postoperative distention, which is undoubtedly aggravated by the effects of anesthesia and preoperative and postoperative medication with morphine, are fairly well accepted, but these authors review in detail the various measures that are indicated and provide an adequate guide for their rational use. A complete discussion of the advantages and disadvantages of gastric suction before and after operation is also to be found in this article. Gastric retention postoperatively frequently has been attributed to the edema associated with hypoproteinemia. That such edema may play an important role when localized in an anastomotic stoma is indisputable. For this reason the attempt by Chauncey and Gray<sup>183</sup> to estimate the actual role played by the concentration of the serum proteins in the production of gastric retention is of interest. These authors studied groups of postoperative patients in whom distention was present or failed to occur after operation was performed on the upper portion of the gastrointestinal tract. They found that the fluctuation in amount of gastric retention was not paralleled in any way by fluctuations in the concentration of serum protein or of the albumin fraction or in the colloidal osmotic pressure of the serum. The retention frequently diminished and disappeared with a coincidental decrease in the osmotic pressure and in the concentration of protein. The presence of clinical edema caused by hypoproteinemia was noticed postoperatively at the same time gastric retention finally disappeared. Such findings would tend to throw doubt on the importance of the role played by hypoproteinemia in postoperative gastric retention. Unfortunately, a proper estimate of other variables conducive to the formation of edema in an operative stoma were not available. These variables would include the degree of activity of the ulcerative process at the time of operation and the actual administration of water and electrolytes in relation to the presence of variations in serum protein.

A realization on the part of surgeons that more rapid mobilization of patients operated on for diseases of the digestive tract may be a proper therapeutic procedure is evidenced in the articles by Joseph<sup>184</sup> and González-Bueno.<sup>185</sup> In a discussion of the treatment of acute dilatation of the stomach following operative procedures, Joseph observed that all patients in whom this condition developed had only one common factor—namely, enforced confinement to bed following the operative procedure. In the presence of acute postoperative gastric dilatation, he has in recent years proceeded to stand the patient upright and aid him in taking a few steps, in spite of obvious postoperative weakness and depletion. The treatment apparently was successful in correcting the condition. González-Bueno<sup>185</sup> goes so

182 Singleton, A. O., Rogers, F., and Houston, F. G. The Problem of Intestinal Gases Complicating Abdominal Surgery, *Ann Surg* **115** 921, 1942.

183 Chauncey, L. R., and Gray, H. K. The Relationship of the Concentration of Proteins in the Serum to Postoperative Gastric Retention, *Gastroenterology* **1** 72, 1943.

184 Joseph, E. G. A New Treatment for Acute Dilatation of the Stomach, *Am J Surg* **60** 381, 1943.

185 González-Bueno, C. Immediate Mobilization of Those Operated on for Disease Conditions of Digestive Tract. Results in Seventy-Four Cases, *Rev clín españ* **6** 405, 1942.

far as to insist that patients should leave the operating table on their own feet. He reviews 74 consecutive laparotomies in which the postoperative treatment was ambulatory, the operations being on the stomach, the biliary tract, the liver or the intestine. Newburger<sup>186</sup> contributes a similar point of view in a study of the influence of exercise on wound healing in rats. Standardized laparotomy wounds were produced in rats at intervals of three, five and ten days. The strength of the wounds was determined in animals which were kept at rest and in others which were exercised. Exercise rather than immobilization was found to hasten the increase in tensile strength of the experimental abdominal incision. Such a conception of postoperative care is worthy of serious thought, even if modifications and exceptions are needed. There can be little doubt that prolonged and absolute immobilization is the ideal procedure for the production of many postoperative complications.

The preceding comments have had chiefly to do with the surgical approach to the problem of ulcer. It is still true that the vast majority of patients with ulcer should be managed by medical procedures, but there is little that is novel or untried in the current literature. Various reports on antacid therapy by the use of alkalis, colloidal aluminum hydroxide and various drip methods are to be found but deserve little more than passing comment. Rossett and Flexner,<sup>187</sup> after continuous recordings of the gastric  $p_H$  in situ, conclude that milk or aluminum hydroxide in adequate dosage best fulfils the physiologic criteria of an ideal antacid. The efficacy of the drip method in the reduction of gastric acidity is reviewed by Cornell and his associates,<sup>188</sup> who claim that this method possesses advantages over the intermittent procedures by a more effective control of night pain, reduction in the time of hospitalization required for healing of the ulcer, and the possibility of administering an adequate diet with simultaneous continuous control of interdigestive gastric secretion. In difficult cases there seems little reason to doubt that the drip method, with use of milk or a colloidal gel, is extremely effective, but there is still reason to believe that it represents an unnecessary refinement in most simple cases of duodenal ulcer.

In view of possible difficulties secondary to the rationing of food, a note by Nye<sup>189</sup> is of passing interest. He stresses the nutritional and also the practical value of a free use of potatoes in the diet for patients with ulcer, because of their large content of minerals and of vitamins A, B<sub>1</sub> and C and their alkaline reaction.

The current use of amino acids, particularly for undernourished, depleted patients suffering from gastrointestinal disease, has led to a study of the effect of the oral administration of a solution of a mixture of amino acids on gastric acidity by Levy and Siler.<sup>190</sup> These authors show that an orally administered mixture of amino acids is an effective buffering agent when introduced into the stomach. Free acid is consistently reduced, and peptic activity is reduced to a minimum. The mixture can be given safely to normal persons without the mildest discomfort, and in the treatment of ulcer, even in the presence of bleeding, its use seems justified.

186 Newburger, B. Early Postoperative Walking. I. The Influence of Exercise on Wound Healing in Rats, *Surgery* **13** 692, 1943.

187 Rossett, N. E., and Flexner, J. A Method for the Continuous Recording of Gastric  $p_H$  in Situ. IV. Further Evaluation of the Efficacy of Antacids in Vitro and in the Human Being, *Ann Int Med* **18** 193, 1943.

188 Cornell, A., Hollander, F., and Winkelstein, A. The Efficacy of the Drip Method in the Reduction of Gastric Acidity, *Am J Digest Dis* **9** 332, 1942.

189 Nye, L. J. J. Potato Diet in Peptic Ulcer, *M J Australia* **1** 7, 1943.

190 Levy, J. S., and Siler, K. A. Clinical Studies of Amino Acids. I. The Effect of Oral Administration of a Solution of an Amino Acids Mixture on Gastric Acidity, *Am J Digest Dis* **9** 354, 1942.

Kirsner and Palmer<sup>191</sup> continued their studies on the alkalosis developing during "Sippy" treatment. The results in a large number of patients with ulcer indicate that alkalosis complicating Sippy treatment with calcium carbonate can be prevented in almost all instances by the concurrent administration of adequate amounts of sodium chloride. The therapeutic action of sodium chloride they attribute largely to the increased excretion of base bicarbonate in the urine, at the expense of the bicarbonate in the blood, after the administration of salt. In occasional cases sodium chloride therapy was apparently not only inadequate to forestall the development of alkalosis but insufficient to correct the acid-base disturbance. They believe it possible that in these few cases insufficient amounts of salt were given and the excretion of the amount of bicarbonate in the urine was retarded by antecedent impairment of renal function. In a separate article<sup>192</sup> they record an unusual incidence of extreme tolerance to massive quantities of sodium bicarbonate. Their case was that of a patient with ulcer who had been twice hospitalized because of massive hemorrhage. Studies of renal function gave normal results, and the administration of 32,000 Gm of sodium bicarbonate in twenty months produced no marked alteration in the acid-base balance and no decrease in the urea clearance.

Warren, Front, and Kirsner<sup>193</sup> studied the effect of antacid therapy on the peptic activity of gastric juice in a group of persons, including several patients with ulcer. Their results indicated that the inhibition of peptic activity in man appears to be related to the increase in  $p_H$  of the gastric juice toward neutrality but that for a given  $p_H$  aluminum hydroxide apparently exerts a greater antipeptic effect than calcium carbonate. The treatment of peptic ulcer with milk and cream, in frequent small feedings, and either calcium carbonate or aluminum hydroxide reduces the peptic activity of human gastric contents.

Confirmation of the results previously reported by Palmer and his associates on the effect of irradiation of gastric acidity is to be found in an article by Jenkins and McGeorge<sup>194</sup>. A heavy dose of intragastric radiation was produced by the use of radium needles secured at the end of a stout rubber tube and swallowed by the patient. Reduction in the acidity and volume of the gastric juices following irradiation was demonstrated in 13 of the 14 patients with ulcer treated, and clinical improvement accompanied chemical changes in the gastric juice. Such a procedure would seem to be unnecessarily clumsy by comparison with the deep roentgen therapy practiced by Palmer, and the results were no better. These authors, like Palmer, found that gastric acidity does not remain at a low level indefinitely after irradiation but that it gradually tends to rise again toward normal.

The effect of endocrine therapy in gastroduodenal ulceration has been investigated in human beings by Abrahamson, Church and Hinton<sup>195</sup>. These authors point out that males and females have an approximately equal number of peptic

191 Kirsner, J. B., and Palmer, W. L. Value of Sodium Chloride in Prevention of Alkalosis During "Sippy" Treatment with Calcium Carbonate, *Arch Int Med* **71** 415 (March) 1943.

192 Kirsner, J. B., and Palmer, W. L. Studies on the Effect of Massive Quantities of Sodium Bicarbonate on the Acid Base Equilibrium and on Renal Function. Report of a Case with Remarkable Tolerance, *Ann Int Med* **18** 100, 1943.

193 Warren, I. A., Front, J., and Kirsner, J. B. The Effect of Antacid Therapy on the Peptic Activity of Gastric Juice in Man, *Gastroenterology* **1** 102, 1943.

194 Jenkins, J. A., and McGeorge, M. Control of Radium for Gastric Acidity, *Arch Int Med* **70** 714 (Nov) 1942.

195 Abrahamson, R. H., Church, R., and Hinton, J. W. Hormone Effects on the Male Gastroduodenal Mucosa, *Am J M Sc* **204** 809, 1942. Abrahamson, R. H., and Hinton, J. W. The Gastric Mucosa as an Endocrine Gland, *Surg, Gynec & Obst* **76** 147, 1943.

ulcers before puberty when their hormonal balance is as yet not well established. Following puberty and synchronously with the change in the androgen-estrogen ratio, the peptic ulcer ratio changes to 9 males per 1 female. Peptic ulcer occurs frequently in females during and immediately following the menopause. Because of these facts, a group of male patients with duodenal ulcer who previously had responded unsuccessfully to other forms of therapy for ulcer for a year or longer were placed on daily injections of varying doses of estrogen substance (estione in oil). The results of this treatment appeared to be favorable in that there was a higher percentage of remissions than is usual in controls (82 per cent). Of greater importance is the fact that healing of the duodenal lesion occurred in nearly half of the subjects, in spite of a definitely increased free and total acidity, a point which casts some doubt on the view concerning the relationship between the healing of a duodenal ulcer and measures directed toward lowering gastric acidity. These same investigators also observed the effect of thyroid and thyroxin medication in a group of patients with ulcer. No conclusive results were obtained.

*Miscellaneous Gastric Conditions*—Miscellaneous and odd gastric lesions are worthy of short comment. A report by Browne and McHardy<sup>196</sup> on the pseudo-cascade stomach is of importance largely in differentiating this condition from the "hourglass" stomach, with which it is frequently confused in the American literature. In a cascade stomach the upper portion of the stomach is a flaccid, posteriorly flopped sac devoid of peristalsis, the lower, and main, portion of the stomach is a normal peristaltic organ. Characteristically the upper portion fills, and the contents cascade over into the lower portion with changes in position, especially when the patient lies on the left side. A transitory type may occur occasionally, due to spasm of the oblique muscle of the stomach, to an organic defect caused by a gas-filled splenic colon displacing an abnormally fixed or ptosed stomach or to a benign or malignant intragastric deformity. The diagnosis is roentgenologic. In the case reported by these authors the cardiac portion of the stomach was markedly distorted and cascading was produced by distention of the splenic flexure with air. A mild superficial gastritis in the cardiac loculus was present. Laparotomy showed adhesions along the lesser curvature and part of the anterior gastric wall, producing a short gastrohepatic ligament and fixation. Section of the adhesions permitted a good recovery and freedom from symptoms a year later. A somewhat similar example of cascade stomach is reported by Charbonnier,<sup>197</sup> in which biloculation of the stomach was caused by the transverse colon pressing against it from behind. At operation, a thick, fibrous band, running from the region of the abdominal wall near the spleen toward the splenic flexure and constricting the descending colon immediately below the flexure, was found. Division of the adhesions immediately reestablished normal gastric and colonic relationships.

Gastric diverticulum is uncommon, although it has been known since 1774. Sixty-five per cent of the diverticula occur in the greater curvature at the cardiac end of the stomach, according to Love,<sup>198</sup> who reports such an anomaly. A detailed study of 35 cases of gastric diverticulum is presented by Tracy.<sup>199</sup> One case in particular is of interest, in which a prepyloric diverticulum caused recurrent gastric obstruction.

196 Browne, D. C., and McHardy, G. Pseudo-Cascade Stomach. Case Report, *Am J Digest Dis* **10** 224, 1943.

197 Charbonnier, A. A Case of Mid-Gastric Occlusion Caused by a Transverse Megacolon of Mechanical Origin, *Gastroenterologia* **67** 55, 1942.

198 Love, McN. Gastric Diverticulum, *Brit J Surg* **30** 180, 1942.

199 Tracey, M. L. Gastric Diverticula, *Gastroenterology* **1** 518, 1943.

Prolapsed gastric mucosa causing symptoms of pyloric obstruction has been recognized by roentgenologists for some years. Diagnoses are not common, however, and accordingly the report of 4 cases by Melamed and Hiller<sup>200</sup> is of interest. In 1 instance severe melena arising from 2 ulcers on the prolapsing mucosa was the first outstanding symptom. One of these ulcers was demonstrated roentgenologically.

Interesting case reports of tuberculosis of the stomach and syphilis of the stomach, respectively, are recorded by Hartz and van der Sar<sup>201</sup> and by Palmer and his associates<sup>202</sup>. Roentgen studies on 225 patients with pellagra are reported by Díaz-Rubio and Roldán<sup>203</sup>. The most noteworthy feature observed by the last-mentioned authors was diminution of gastric peristalsis, which often gave rise to great dilatation and retarded evacuation of gastric contents. The mucosa was atrophic in over two thirds of the cases, but in about one fourth the roentgenologic appearance of the stomach was normal as regards tonus, peristalsis, evacuation and mucosal relief, in spite of the fact that pellagra was fully developed. There were some cases in which no relationship existed between the severity of the changes and the gravity of the clinical picture, but in 59 patients, on whom at least three studies were made, there was a close parallelism between the clinical picture and the intensity of the roentgenologic signs.

Autopsy studies on the stomachs of patients dying from pernicious anemia were made by Cox<sup>204</sup>. In 2 instances the patients had had continuous successful liver therapy for ten and thirteen years, respectively, and there was no anemia at the time of death. Results of the examinations showed that almost complete replacement of the normal mucosal glands, of the fundic type, by abnormal, less differentiated glands had taken place. The pyloric zone was only slightly altered. No relationship could be found between the appearance of the stomach and the duration of the disease or of the treatment. The stomach from a well studied case of long-standing sprue with fatal macrocytic anemia showed no comparable change. The authors suggest that the gastric lesions in cases of pernicious anemia are different from those accompanying other diseases and may represent a specific change, possibly the result of massive destruction of the highly differentiated parietal and chief cells. Such histologic observations are of interest inasmuch as they indicate that the gross regeneration of the gastric mucosa, which can be readily demonstrated by gastroscopy following successful therapy of pernicious anemia, must represent a replacement of the highly differentiated mucosal cells by others that are functionally different. The difference between these changes in pernicious anemia and those occurring in sprue are commented on in detail by Ollerios<sup>205</sup>. Like patients with pernicious anemia, the vast majority of patients with tropical sprue show invasion of the stomach by the gram-negative flora of the large intestine. The mucosal atrophy observed in the gastroscopic examination of patients with sprue is less marked than that occurring in pernicious anemia in temperate climates. Patients with tropical sprue eliminate neutral red by the

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200 Melamed, A, and Hiller, R. I. Prolapsed Gastric Mucosa. Roentgenologic Demonstration of Ulcer Crater in Prolapsed Polypoid Mucosa, *Am J Digest Dis* **10** 93, 1943.

201 Hartz, P. H., and van der Sar, A. Ulcerative Tuberculosis of the Stomach, *Am Rev Tuberc* **47** 46, 1943.

202 Palmer, W. L., Schindler, R., Templeton, F. E., and Humphreys, E. M. Syphilis of the Stomach. A Case Report, *Ann Int Med* **18** 393, 1943.

203 Díaz-Rubio, M., and Lara Roldán, L. Casal's Disease. Roentgen Behavior of Stomach in Pellagra, *Rev clin españ* **4** 408, 1942.

204 Cox, A. J. The Stomach in Pernicious Anemia, *Am J Path* **19** 491, 1943.

205 Rodríguez Ollerios, A. Gastric Similarities and Differences Between Tropical Sprue and Pernicious Anemia, *Am J Digest Dis* **9** 261, 1942.

gastric mucosa, even when there exists a histamine-resistant achylia. This is suggested by the author as a means of differentiating between tropical sprue and pernicious anemia.

*Cancer of the Stomach*—The difficulty in obtaining early diagnoses of gastric cancer is a perennial one. Too frequently the diagnosis is not made early because of carelessness and an inadequate history. Some of the difficulties in the roentgenologic diagnosis of gastric cancer are outlined by Kirklin,<sup>206</sup> who presents a thorough discussion of the entire subject of roentgenologic diagnosis of gastric cancer. He correctly points out that roentgen examination will exhibit any gastric lesion that is capable of producing symptoms or that can be seen macroscopically, and failure to discern it should be charged to the examiner, not to the method. Cancer of the cardia is particularly likely to be missed unless the region of the gas bubble is inspected closely. More common are the failures or mistakes in differential diagnosis of cancer from benign lesions. Kirklin states that most misunderstandings could be avoided if to the roentgenologic diagnosis of benign tumor were added the caution that such tumors are partly malignant, and to the diagnosis of gastric ulcer the reminder that about one tenth of such ulcers, even though they appear roentgenologically benign, are cancerous.

The gastroscopic diagnosis of gastric cancer, although a tremendous additional help, is also subject to serious error. Schiff<sup>207</sup> discusses gastroscopic examinations in 78 cases of proved gastric cancer. In 53 cases the lesion was seen and correctly diagnosed, and in 7 gastroscopic examination was the sole means of revealing the presence of the tumor. In 17 instances technical difficulties prevented visualization of the lesion, and in 9 it was mistaken for a benign gastric ulcer. Similar difficulties are reported by Freedman and his associates,<sup>208</sup> who record 5 cases in which the roentgenologic and gastroscopic appearance of localized chronic hypertrophic gastritis simulated carcinoma of the stomach. Moersch and Weir<sup>209</sup> cite an unusual difficulty confronting the gastroscopist, namely, differentiation between prolapsed mucosa and gastric carcinoma.

The question of the causation of gastric cancer is discussed by various investigators and clinicians. Nettleship<sup>210</sup> points out the peculiarities of the gastric mucosa of man and compares it with that of other species. The precancerous conditions of the mucosa are then described, and special consideration is given to the concept of the possible origin of gastric cancer from a chronically damaged mucosa. The author expresses the belief that long time factors are involved in the production of human cancer and assumes that this time factor will have to be duplicated experimentally. Experimental agents must be used to stimulate those conditions of the gastric mucosa most commonly found associated with human gastric cancer, i. e. polyps, chronic gastritis and ulcer. Stout<sup>211</sup> focuses attention on the precancerous stomach, the gross forms assumed by early carcinoma, its method of spread and its differentiation from other kinds of gastric lesions. On the basis of an examination of over 400 specimens, he states that it is entirely

206 Kirklin, B. R. Mistakes and Misunderstandings in the Roentgenologic Diagnosis of Gastric Cancer, *Arch Surg* 46 861 (June) 1943.

207 Schiff, L. Gastroscopic Diagnosis of Gastric Cancer, *Arch Surg* 46 865 (June) 1943.

208 Freedman, E., Glenn, P. M., and Laipply, T. C. Chronic Gastritis Simulating Gastric Carcinoma. Report of Five Cases, *Arch Int Med* 71 23 (Jan.) 1943.

209 Moersch, H. J., and Weir, J. F. Redundant Gastric Mucosa Simulating Carcinoma of the Stomach, *Am J Digest Dis* 9 287, 1942.

210 Nettleship, A. Experimental Gastric Carcinoma, *Arch Surg* 46 793 (June) 1943.

211 Stout, A. P. Pathology of Carcinoma of the Stomach, *Arch Surg* 46 807 (June) 1943.

unknown and unproved whether or not there is a consequential relationship between so-called chronic gastritis and its glandular changes and gastric cancer. He too stresses the importance of the directional growth in different carcinomas and the need for looking for cancer in stomachs with gastritis, peptic ulcer or adenomatous polyps.

The relationship between cancer and atrophic gastritis has been stressed by Schindler and others, but, as already noted, no causative connection has been found between the two conditions. Guiss and Stewart<sup>212</sup> conclude, from a study made on a large number of stomachs obtained immediately or a few hours after death, that the claim that chronic atrophic gastritis is a precancerous lesion is unsupported by their observations. Atrophic changes in the stomach represent a common condition of advanced age, and both atrophy and cancer appear to be common in aging organs, but no causal relationship was found. Judd<sup>213</sup> also has undertaken a histologic study of the residual lesions of ulcerative gastritis, in trying to determine a possible relationship to the development of cancer. In addition to the microscopic study of 200 carcinomas of the stomach removed at operation or necropsy or both, 78 control specimens obtained from a "younger" and a "comparable" age group were examined. The frequent occurrence of certain residual lesions in carcinomatous stomachs was compared to the occurrence of such lesions in non-carcinomatous stomachs. The fundamental difference between the two is the relative lack of mucous cell hyperplasia in the latter. Essentially similar lesions occurring at a distance from a gastric carcinoma suggested to the author that the entire gastric mucosa had undergone change and that much time had been taken for this to occur. He concludes that carcinoma develops in a previously damaged stomach. An interesting observation is that reported by Jankelson and associates<sup>214</sup> in a study of the relationship between atrophic gastric mucosa and carcinoma of the stomach. Eighteen patients, chiefly women between the ages of 30 and 50, were carefully studied over two years, and no other pathologic change than the atrophic gastritis was found. In 2 instances a polyp developed during the period of observation. Such an occurrence is remarkable and warrants the authors' conclusion that atrophy of the gastric mucosa, with or without pernicious anemia, should be considered as a potential precancerous lesion. They believe that the development of a cancer of the stomach is probably by way of a polyp and is almost invariably preceded by achlorhydria. An additional study was made of 100 clinically proved cases of pernicious anemia, in which were found 4 proved cases of cancer of the stomach. Doehring and Eusterman<sup>215</sup> report 17 cases of cancer of the stomach encountered in a total of 1,014 cases of pernicious anemia, an incidence of 1.7 per cent. The development of pernicious anemia preceded the diagnosis of cancer by an average interval of almost nine years, a fact that probably accounts for the present increasing frequency of gastric cancer in association with pernicious anemia. An unusual occurrence is that reported by White<sup>216</sup> of simultaneous cancer and tuberculosis of the stomach in a case of pernicious anemia.

212 Guiss, L. W., and Stewart, F. W. Chronic Atrophic Gastritis and Cancer of the Stomach, *Arch Surg* **46** 823 (June) 1943.

213 Judd, E. S., Jr. Residual Lesions of Ulcerative Gastritis. Possible Relationship to the Development of Carcinoma of the Stomach, *Surg., Gynec. & Obst.* **75** 424, 1942.

214 Jankelson, I. R., McClure, C. W., and Freedberg, H. Relation of Atrophic Gastric Mucosa to Carcinoma of the Stomach, *Rev Gastroenterol* **10** 26, 1943.

215 Doehring, P. C., and Eusterman, G. B. Association of Pernicious Anemia and Carcinoma of the Stomach, *Arch Surg* **45** 554 (Oct.) 1942.

216 White, R. R. Simultaneous Carcinoma and Tuberculosis of the Stomach in a Case of Pernicious Anemia, *Proc Staff Meet., Mayo Clin* **18** 165, 1943.



The latter condition had existed for twenty years prior to the development of the two superimposed conditions

An autopsy study by Saphir and Parker<sup>217</sup> on the linitis plastica type of carcinoma was undertaken to see whether the investigation of a large amount of autopsy material would disclose diseases other than carcinoma which might cause linitis plastica. They arrived at the conclusion that it is questionable whether linitis plastica, in the sense of a purely inflammatory lesion, exists. No single instance was observed among 6,520 autopsies. In the 26 cases of carcinoma of the stomach of the linitis plastica type, careful histologic studies were made, and the details are given in the article, the chief characteristics being the presence of subacute and chronic inflammation, with much fibrosis and hyalinization. An important clinical fact brought out is the notation that the interval between the onset of symptoms referable to gastric disorders and death in these cases was uncommonly short as compared with that in the control group of cases of miscellaneous gastric carcinomas, also, that the postoperative survival period of 15 patients who were operated on seemed extremely short, eleven days or less.

An important estimate of the prognosis and end results in the treatment of cancer of the stomach is to be found in an article by Walters, Gray and Priestley<sup>218</sup>. In a series of 10,890 cases observed at the Mayo Clinic slightly more than half the patients were considered to be operable, a figure that in recent years has risen to about two thirds of those presenting themselves with this malady. About one quarter of the patients in the large series considered operable were found to have removable lesions, although in 1942 this was true of only one third of the number. The recent mortality rate was just under 11 per cent. Of those patients who underwent resection and survived the immediate postoperative period, nearly 30 per cent were alive at the end of five years, and over 6 per cent lived twenty-five years or longer. These figures show the increasingly favorable prognosis for this serious disease once the diagnosis is established.

The results of surgical treatment for cancer of the cardiac end of the stomach have been immeasurably improved since the introduction of transthoracic resection of these tumors. Churchill and Sweet<sup>219</sup> report 21 cases in which a tumor at the junction of the stomach and the esophagus was operated on by the transthoracic approach. Resection of the growth was done in 13 cases, with an esophagogastric anastomosis in 11, 8 patients were well and free of symptoms from two months to two and one-half years after the operation.

A rather surprising record of surgical success in the treatment of cancer of the stomach in aged persons is presented by Bowers<sup>220</sup>. He reports operative procedures on 104 persons who were over 60 years of age. The mortality rate following resection was 9 per cent for those over 60. From a study of 9 illustrative cases, Bowers believes that far from hopeless results may be anticipated in aged patients with carcinoma of the stomach, and that with early recognition of the condition and proper preparation, operation can be safely done with results, if anything, better than in younger age groups. That the most radical form of gastric

217 Saphir, O, and Parker, M. L. Linitis Plastica Type of Carcinoma, Surg, Gynec & Obst **76** 206, 1943

218 Walters, W, Gray, H. K., and Priestley, J. T. Prognosis and End Results in the Treatment of Cancer of the Stomach, Arch Surg **46** 939 (June) 1943

219 Churchill, E. D., and Sweet, R. H. Transthoracic Resection of Tumors of the Stomach and Esophagus, Ann Surg **115** 897, 1942, **116** 566, 1942

220 Bowers, R. F. The Surgical Treatment of Carcinoma of the Stomach in Aged Individuals, Surgery **11**:869, 1942



operation is possible in the aged is evident from the report of Gillespie,<sup>221</sup> who operated on a man of 79 for carcinoma of the stomach and performed a total gastrectomy. The patient made an uneventful convalescence.

Less than 150 cases of true total gastrectomy for cancer have been reported. That such an operation is consistent with a relatively long survival period is evident from 2 cases reported by Joll and Adler.<sup>222</sup> Survival times of three years and two months, and two years and six months are reported in 2 of these authors' cases, in which the entire stomach, including the distal portion of the esophagus and the proximal portion of the duodenum, was removed because of cancer.

For patients considered inoperable, radiation therapy may achieve palliation of symptoms. Raven<sup>223</sup> reports 34 cases in which the disease was so advanced that only palliative measures were possible. Radon seeds were implanted in the growth at laparotomy, and the abdomen was closed without drainage. Radiation sickness was common owing to the close proximity of other vital organs, but life was apparently prolonged well beyond the period that would have been expected had the patients received no treatment. Symptoms were relieved in many instances. Three patients survived more than one year.

Acute perforation of gastric cancer is relatively uncommon. By 1935, about 80 cases had been reported. García Barón<sup>224</sup> was able to find only 3 perforations of cancer in a twelve year period, although at the same time 400 cases of perforated ulcer were encountered. Surgical intervention with closure is the obvious procedure.

A curious clinical note is that of Cardon,<sup>225</sup> who tells of a case of intractable generalized pruritus of three years' duration in an elderly person in whom carcinoma of the stomach was finally discovered. The itching of the skin was cured by successful surgical removal of the cancer.

Certain fundamental metabolic studies on patients with cancer of the gastrointestinal tract have been made by Ariel and his collaborators.<sup>226</sup> In one reported study 6 patients with neoplastic lesions of the extremities were used as controls and 6 patients with gastrointestinal cancer were studied by means of the aminoacetic acid tolerance test. Delayed absorption of aminoacetic acid followed the ingestion of 25 Gm of that amino acid, and high peaks of plasma amino acid nitrogen curves were obtained for patients with gastric cancer, which suggest a delayed rate of utilization. After removal of the stomach from a patient with a gastric cancer, a rapid high peak of the plasma amino acid curve was obtained, this indicates that the presence of the cancer contributed to the slow absorption but not to the impaired utilization of aminoacetic acid. The defective absorption and metabolism of the end product of protein digestion in patients with gastric cancer may contribute to the hypoproteinemia so frequently exhibited by these patients. In another article, the authors conclude that patients with gastrointestinal

221 Gillespie, M. G. Gastrectomy for Carcinoma. Case Report of Oldest Patient to Survive, *Am J Surg* **57** 348, 1942.

222 Joll, C. A., and Adler, D. I. Long Survival After Total Gastrectomy. A Brief Review with a Report of Two Cases, *Brit M J* **2** 632, 1942.

223 Raven, R. W. Inoperable Gastric Cancer. Treatment with Radon Seeds, *Lancet* **2** 335, 1942.

224 García Barón, A. Acute Perforations of Malignant Tumors of the Stomach, *Rev Clin españ* **5** 96, 1942.

225 Cardon, L. Generalized Pruritus Due to Carcinoma of the Stomach and Cured by Gastrectomy, *Am J Digest Dis* **10** 63, 1943.

226 Ariel, I., Jones, F., Pack, G. T., and Rhoads, C. P. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. XII. The Glycine Tolerance Test in Patients with Gastric Cancer, *Ann Surg* **117** 740, 1943. Abels, J. C., Ariel, I., Rekers, P. E., Pack, G. T., and Rhoads, C. P. Metabolic Abnormalities in Patients with Cancer of the Gastrointestinal Tract. A Review of Recent Studies, *Arch Surg* **46** 844 (June) 1943.

carcinoma suffer from several metabolic abnormalities which may endanger their operative and postoperative course. Many of these abnormalities probably are related to hepatic insufficiency, which probably is induced by the presence of the gastrointestinal neoplasm. The removal of the cancer often is followed by a disappearance of the metabolic dyscrasias, principally that which involves the fabrication of serum protein. However, hypoproteinemia is a frequent occurrence and may persist well into the postoperative period. Total, and perhaps subtotal, gastric resection, although necessary for the surgical treatment of the patient, may institute a new metabolic disturbance, steatorrhea and consequent loss of weight. The importance of replacement therapy for such conditions is obvious.

*Noncancerous Tumors of the Stomach*—Because of the relatively infrequent occurrence of noncancerous tumors of the stomach and the difficulties inherent in their diagnosis, reference will be made to the following articles. Multiple gastric polyps present no characteristic symptoms, but epigastric pain and tenderness appear to be rather common, and bleeding occurs as a frequent concomitant. A total of 121 such cases culled from the literature is reviewed by Pearl and Brunn.<sup>227</sup> Symptoms of pyloric obstruction were encountered, and several patients had noted symptoms over more than twenty years. The condition was frequently overlooked by the roentgenologist. Malignant degeneration was common.

The existence of diarrhea in association with a benign tumor of the stomach has been frequently noted. Proof that the gastric lesion is the cause of the intestinal symptom, however, is usually not possible. Culver and his associates<sup>228</sup> cite the case of a woman of 35 who complained of persistent diarrhea for one year prior to the diagnosis of a benign polypoid tumor of the stomach. Surgical resection was followed by good recovery and complete cessation of symptoms.

The relatively frequent occurrence of gastrointestinal bleeding in the presence of intraluminal tumors of the stomach is emphasized by Sahler and Hampton<sup>229</sup> in an excellent article dealing principally with the diagnostic features to be shown by the roentgenologist. The discussion is based on a study of 24 intramural gastric tumors, including leiomyoma, leiomyosarcoma, fibroma, fibrosarcoma and lymphoma. In all but 3 cases there were fairly adequate roentgen examinations. Bleeding was the most important common symptom. The diagnostic value of gastroscopy is stressed.

O'Donogue and Jacobs<sup>230</sup> review the literature on lymphosarcoma of the stomach, of which less than 500 cases have been recorded. A case report is given of a patient in whom an erroneous preoperative diagnosis was made of cancer of the stomach. The resected specimen showed reticulum cell sarcoma, a form constituting about half of all lymphosarcomas of the stomach. The authors conclude that lymphosarcoma constitutes from 1 to 2 per cent of all gastric malignant growths, that it occurs at an earlier period of life than does carcinoma, that it metastasizes late and that it responds more favorably to surgical removal than does carcinoma. Recognition of lymphosarcoma of the stomach secondary to a distant focus is difficult, but such recognition is important because of the wisdom

227 Pearl, F. L., and Brunn, H. Multiple Gastric Polyposis. A Supplemental Report of Forty-One Cases Including Three New Personal Cases, *Surg., Gynec. & Obst.* **76**:257, 1943.

228 Culver, G. J., Westinghouse, W., and Koenig, E. C. Report of a Case of Benign Gastric Polyp Producing a Gastrogenic Diarrhea, *Ann. Int. Med.* **17**:1015, 1942.

229 Sahler, O. D., and Hampton, A. O. Bleeding Associated with Extra Mucosal Tumor of the Stomach, *Am. J. Roentgenol.* **49**:442, 1943.

230 O'Donogue, J. B., and Jacobs, M. B. Lymphosarcoma of the Stomach. Report of a Case with Some Clinicopathological Notations, *Am. J. Surg.* **58**:246, 1942.

of avoiding unnecessary surgical intervention in cases of this condition. Three cases, 1 of the authors' own, are reviewed by Buschke and Cantril.<sup>231</sup>

An extremely rare condition is reported by Selman,<sup>232</sup> who operated successfully on a benign tridermal teratoma in a child 4 months old.

A presentation by Lemmer<sup>233</sup> of the case of a 44 year old woman who was found to have a carcinoid tumor of the stomach is mentioned to call attention to the occurrence of a fairly common type of tumor in an uncommon location.

*Unusual Tumors of the Small Bowel*—Nonulcerative disease of the duodenum is not particularly common, and in many instances anatomic variations from the normal, though demonstrable, produce no symptoms. Certain conditions, however, are noted from time to time that are the cause of more or less serious symptoms and for this reason warrant mention. Congenital atresia of the duodenum is far from common, and successful surgical intervention for it is still rare. Ward and Cooper<sup>234</sup> report a successful duodenoduodenostomy on a newborn infant for atresia of the second portion of the duodenum. Only 14 instances of survival have been reported in the literature on this condition. The results of the operation were successful, and the clinical improvement in this case is in marked contrast to the result of any kind of surgical treatment of so-called duodenal ileus. A similar example of the same condition is reported by Wigg and Clagett,<sup>235</sup> in which a successful posterior gastroenterostomy was performed on a 15 day old infant. Atresia was not absolutely complete in this instance and involved the lower portion of the duodenum. A third instance of complete atresia is reported by Impink and Clammer.<sup>236</sup> In this instance, a duodenojejunostomy performed fifty hours after birth was unsuccessful because of pulmonary complications.

Dilatation of the bowel and hypertrophy of its walls in the absence of obstruction or inflammation occur in cases of megacolon, but a similar condition in the small intestine is most unusual. Such a case is described by Brown and Pemberton.<sup>237</sup> Three years after an operation for a correctly diagnosed duodenal ulcer, a new type of abdominal distress, midabdominal pain not relieved by food, was observed, and a roentgen examination at this time showed slight dilatation of the distal portion of the duodenum. Because of the persistence of symptoms in spite of treatment, an operation was done, and an enteroanastomosis was made between the first part of the jejunum, which was dilated, and a normal lower portion. After the operation symptoms continued and vomiting increased. Roentgen examination after a barium sulfate meal showed dilatation of the entire jejunum, more marked than before operation. Subsequently a third operation was performed, with resection of 78 cm of enormously dilated jejunum. The specimens showed subacute jejunitis with multiple ulcerations. It could not be determined whether the abnormal condition of the duodenum and jejunum was a primary dilatation and hypertrophy or whether it was an inflammatory process.

231 Buschke, F, and Cantril, S. T. Secondary Lymphosarcoma of the Stomach, *Am J Roentgenol* **49** 450, 1942.

232 Selman, A. N. Complex Tridermal Teratoma of the Stomach (Benign). Case Report, *Am J Surg* **59** 567, 1943.

233 Lemmer, K. E. Carcinoid Tumors of the Stomach, *Surgery* **12** 378, 1942.

234 Ward, C. S., Jr., and Cooper, F. W., Jr. Atresia of the Duodenum. Case Successfully Treated by Duodenoduodenostomy, *Ann Surg* **117** 718, 1943.

235 Wigg, L. M., and Clagett, O. T. Congenital Atresia of the Duodenum. Report of a Case, *Proc Staff Meet, Mayo Clin* **17** 577, 1942.

236 Impink, R. R., and Clammer, G. R. Atresia of the Duodenum. Case Report. *Ann Surg* **116** 334, 1942.

237 Brown, P. W., and Pemberton, J. DeJ. Megaduodenum and Megajejunum. *Proc Staff Meet, Mayo Clin* **18** 109, 1943.

An exceedingly rare cause of pain arising from partial obstruction in the duodenum is described by Brooks and Weinstein.<sup>238</sup> Nausea, vomiting and questionable jaundice caused the patient to enter the hospital fifteen years after an acute cholecystitis with drainage. The recurrent attacks of nausea and vomiting prior to his admission at this time were thought to be due to a peptic ulcer, but because of the severity of the symptoms exploration was done. The first 2 feet (60 cm) of the jejunum showed marked hypertrophy and dilatation. One inch (2.5 cm) from the pylorus was a large polypoid mass, which when delivered through the incision in the duodenum was found to be attached to the posterior wall of the descending portion of the duodenum. The tumor appeared to be a cyst of the ampulla of Vater, with symptoms due to intussusception of the cyst.

An equally unusual cause for vague epigastric distress associated with diarrhea and occult blood in the stools is described by Shackleford and his associates.<sup>239</sup> At operation the patient was found to have metastatic myosarcoma of the ampullary portion of the duodenum. She had had a myosarcoma of the uterus removed four years before. The operation was immediately successful.

Carcinoma of the duodenum has been reported from time to time but is infrequent enough to warrant mention. Three cases are reported: 1 case of carcinoma of the duodenal bulb, and 2 of carcinoma involving the third (infra-papillary) portion of the duodenum, by Hartzell,<sup>240</sup> Berger and Koppelman,<sup>241</sup> and Duff and his associates,<sup>242</sup> respectively. The majority of such tumors are around the papillae of Vater.

Three cases of primary adenocarcinoma of the jejunum (Sangster<sup>243</sup>, Kahn and Bay<sup>244</sup>) may be added to the gradually increasing list of these rather uncommon tumors.

The roentgen diagnosis of lesions involving the ileum, the cecum and the proximal portion of the ascending colon is discussed by Pendergrass and Chamberlin.<sup>245</sup> The authors present a few instances in which the clinical and roentgen findings were equivocal as regards the diagnosis of early lesions involving this area. They suggest certain points noted in their cases, which may be of aid in the proper analysis of similar problem cases. Three methods of study are described as ways of arriving at a precise diagnosis: roentgen examination after a barium sulfate meal, examination after an opaque double contrast enema, and study of the intestine with the Miller-Abbott tube.

Only in recent years has it been recognized that argentaffine tumors may produce clinical symptoms and assume all the properties of malignant growths. It is not generally accepted that carcinoid tumors arise from the crypts of Lieberkuhn. These cells are found throughout the gastrointestinal tract but are most abundant in the appendix and the terminal portion of the ileum. Interesting case

238 Brooks, B., and Weinstein, A. Cyst of Ampulla of Vater. Case Report, *Ann Surg* **117** 728, 1943.

239 Shackleford, R. T., Fisher, A. M., and Firor, W. R. Duodenal Tumor of Unusual Character, *Ann Surg* **116** 864, 1942.

240 Hartzell, H. V. A Case of Carcinoma of the Duodenal Bulb Diagnosed Pre-operatively, *Radiology* **39** 474, 1942.

241 Berger, L., and Koppelman, H. Primary Carcinoma of the Duodenum, *Ann Surg* **116** 738, 1942.

242 Duff, G. L., Foster, H. L., and Bryan, W. W. Primary Carcinoma of the Infra-Ampullary Portion of the Duodenum, with Example of Probable Origin from Aberrant Pancreatic Tissue, *Arch Surg* **46** 494 (April) 1943.

243 Sangster, A. H. Case of Adenocarcinoma of the Jejunum, *Brit M J* **1** 12, 1943.

244 Kahn, M., and Bay, M. W. Carcinoma of the Jejunum, *Am J Surg* **58** 145, 1942.

245 Pendergrass, E. P., and Chamberlin, G. W. The Roentgen Diagnosis of Lesions Involving the Ileum, Cecum and Proximal Ascending Colon, *Am J Roentgenol* **48** 16, 1942.

reports of single and multiple tumors of this nature by Pennington and Priestley,<sup>246</sup> Miller and Herrmann<sup>247</sup> and Gold and Grayzel<sup>248</sup> may be mentioned

Records of other rare tumors of the small intestine include cases of hemangioma of the ileum,<sup>249</sup> metastatic melanotic sarcoma of the ileum<sup>250</sup> and primary Hodgkin's sarcoma of the jejunum.<sup>251</sup> In addition to several individual case reports of primary lymphosarcoma,<sup>252</sup> a fairly complete discussion of this type of disease is presented by Usher and Dixon<sup>253</sup> and by Weber, Kirklin and Pugh.<sup>254</sup> The incidence of lymphosarcoma is discussed, over one third of the growths being found in the jejunum and ileum and the remainder in the colon. Colicky pain, loss of weight, anemia and a palpable abdominal mass are fairly characteristic symptoms. Ulcer and perforation are rare and intussusception infrequent. Chronic or subacute obstruction is not uncommon, this is not surprising, since the average diameter of the tumors reported is between 5 and 10 cm. The best prognosis seems to be for lymphosarcoma of the cecum. The details of roentgenologic diagnosis are included in the second article mentioned, but the authors are careful to conclude that they can offer no suggestions as to how roentgenologically to distinguish lymphoblastoma from other lesions of the gastrointestinal tract.

*Regional Ileitis*—The consensus at present seems to be that regional ileitis is essentially a surgical disease. The diagnosis is dependent almost entirely on adequate roentgenologic studies, although the clinical course at times is very suggestive. Both Sussman and Wachtel<sup>255</sup> and Strombeck<sup>256</sup> emphasize striking differences in the picture obtained in the acute and chronic phases. The former authors believe that roentgenologic differentiation from a deficiency pattern is difficult in the acute phase of the disease, but Strombeck states flatly that acute ileitis has a characteristic roentgen picture. The latter describes the findings in detail and states that in acute ileitis the outline of the mucous membrane in the last 10 to 15 cm of the ileum is uneven and edematous. The mucosal swelling is most pronounced next to Bauhin's valve, the two lips of which sometimes are considerably swollen and bulge into the cecum. The mucosal relief in the terminal portion of the ileum is high and irregular, and a walnut-sized filling defect is seen at the site of the valve. He states that roentgen examination can be of great value in differentiating acute appendicitis from acute simple terminal ileitis in

246 Pennington, R. E., and Priestley, J. T. Multiple Carcinoid Tumors of Small Intestine. Report of Case, Proc Staff Meet, Mayo Clin **18** 49, 1943.

247 Miller, E. R., and Herrmann, W. W. Argentaffin Tumors of the Small Bowel. Radiology **39** 214, 1942.

248 Gold, I. R., and Grayzel, D. M. Multiple Argentaffinomas in Ileum with Metastases in Lymph Nodes and in the Liver, Am J Surg **60** 144, 1943.

249 Christopher, F. Hemangioma of the Ileum, Ann Surg **116** 945, 1942.

250 Phillips, J. R. Metastatic Melanotic Sarcoma to the Ileum Causing Intussusception. Am J Digest Dis **10** 147, 1943.

251 Badia, P. D. Primary Hodgkin's Sarcoma of the Jejunum with Perforation, Resection and Radiotherapy Case, Am J Surg **59** 577, 1943.

252 Charache, H. Primary Lymphosarcoma of the Intestine in a Boy of Seven. Follow Up Nine Years, Am J Surg **59** 601, 1943. Borden, D. L., and Taylor, F. D. Primary Lymphosarcoma of the Small Intestine. Case Report, Mil Surgeon **92** 255, 1943. Menne, F. R., Mason, D. G., and Johnston, R. Lymphosarcoma of the Intestine. Report of Two Cases, Arch Surg **45** 945 (Dec) 1942.

253 Usher, F. C., and Dixon, C. F. Lymphosarcoma of the Intestines, Gastroenterology **1** 160, 1943.

254 Weber, H. M., Kirklin, B. R., and Pugh, D. G. Lymphoblastoma Primary in the Gastrointestinal Tract, Am J Roentgenol **48** 27, 1942.

255 Sussman, M. L., and Wachtel, E. Granulomatous Jejuno-Ileitis, Radiology **39** 48, 1942.

256 Strombeck, J. P. Terminal Ileitis and Its Roentgen Picture, Acta radiol **22** 827, 1941.

children and young people, but it is probable that most clinicians would prefer to avoid the use of barium sulfate under such acute conditions. The chronic stenosing form of the disease is more easily diagnosed in most instances, except when it is necessary to rule out ileocecal tuberculosis.

Ginzburg and Garlock<sup>257</sup> state that much of the confusion surrounding indications for therapy (medical versus surgical treatment) of this disease arises from the failure to differentiate between the localized form, which is confined to the distal 4 or 5 feet of ileum, and the more generalized type, in which the distal involvement is only part of a generalized enteritis. They suggest that the term "distal ileitis" be substituted for "regional ileitis," and they believe that this type is essentially amenable to surgical treatment. On the basis of their own experience they believe that the symptoms of "distal ileitis," as a rule, are markedly ameliorated by ileocolostomy with exclusion, rather than resection. Lahey and Sanderson<sup>258</sup> definitely prefer radical resection for the ileum, ascending colon and hepatic flexure as the treatment of choice, and this view is generally held among surgeons.

A plea for conservatism in the surgical management of acute regional enteritis is voiced by Smithy,<sup>259</sup> who reports on a small group of patients managed by simple exploration and appendectomy. None showed progression of the disease. He states, as do others, that a strong tendency toward spontaneous healing is present in certain instances of acute regional enteritis, and he advocates conservative management in many cases. He makes the reasonable suggestion that in order to detect the occasional case in which there is a tendency for the condition to progress to chronic regional enteritis, conscientious observation and frequent postoperative roentgen study are essential in cases of acute enteritis managed by simple exploration and appendectomy.

In Crohn's extensive experience, this disease almost invariably begins in the distal part of the ileum and progresses proximally. For this reason, the report by Johnson<sup>260</sup> is of interest. In his case, the patient, a Negro, had progressive symptoms leading to operation, which showed multiple areas of involvement from that portion of the jejunum just below the ligament of Treitz, extending down for some distance in the upper part of the jejunum. Apparently the disease progressed distally and produced symptoms of obstruction but remained localized to a relatively short segment, even after a six-year period. Crohn comments on this case as being unusual and cites another reported from China.

Studies on absorption of fat and of vitamin A in sprue and in jejunoileitis by Adlersberg and Sobotka<sup>261</sup> suggest a basic difference in fat absorption between sprue and inflammatory disease of the small intestine. In contrast to persons with sprue, patients with extensive granulomatous jejunoileitis had a fairly satisfactory absorption of fat and of vitamin A, and because of this fact the authors believe that in certain borderline cases in which the differential diagnosis is difficult an additional diagnostic point is available.

Relatively little attention has been given in the literature to anorectal findings in cases of regional ileitis. In the article by Sussman and Wachtel, already

257 Ginzburg, L, and Garlock, J. H. Regional Ileitis, *Ann Surg* **116** 906, 1942.

258 Lahey, F. H, and Sanderson, E. Lesions of the Right Colon Involving Right Colectomy, *J. A. M. A.* **120** 1356 (Dec. 26) 1942.

259 Smithy, H. G. Conservation in the Surgical Management of Acute Regional Enteritis, *Surgery* **13** 122, 1943.

260 Johnson, W. R. Chronic, Non-Specific Jejunitis with Unusual Features, *Gastroenterology* **1**:347, 1943.

261 Adlersberg, D, and Sobotka, H. Fat and Vitamin A Absorption in Sprue and Jejuno-Ileitis, *Gastroenterology* **1** 357, 1943.

alluded to, 1 instance is reported in which inflammation was seen proctoscopically. Jackman and Smith<sup>202</sup> review 114 consecutive cases of regional ileitis in which the diagnosis was made by roentgenologic examination confirmed by exploration and in which sigmoidoscopic examinations were made. Ulceration of the lower part of the bowel was found after short-circuiting operations. One third of the patients had an anal abscess or an anal fistula or gave a history of having had an operation for a fistula, the ileitis remaining undiscovered until a later date. In almost one fifth of the cases an extraectal mass was found, in 8 cases anal ulceration or a contracted anal outlet was found, 4 patients had ulceration of the lower part of the bowel after short-circuiting operations and resection of the diseased portion of the bowel. The combination of an anal abscess or fistula and vague intestinal disturbances in a young adult should make the clinician suspect the possibility of regional ileitis.

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262 Jackman, R. J., and Smith, N. D. Some Manifestations of Regional Ileitis Observed Sigmoidoscopically, Surg., Gynec. & Obst. 76:444, 1943

*(To Be Continued)*



# News and Comment

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## GENERAL NEWS

**Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation**—Eighteen applications for grants were received by the Trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation during 1943. Thirteen of these came from the United States and the other five from five different countries in Europe, Asia and North and South America.

In the twenty years of its existence the Foundation has made four hundred and eighty-one grants, which have been distributed to scientists throughout the world.

The purposes for which the Fund may be used are mentioned in the January 1942 issue of the *ARCHIVES*, page 159.

Applications for grants to be held during the year 1944-1945 should be sent to Dr Joseph C Aub, Massachusetts General Hospital, Fruit Street, Boston, and must be in his hands before April 1944. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, include an accurate description of the research and give the size of the grant requested and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done.

## SOCIETY NEWS

**Mississippi Valley Medical Society**—The tenth annual meeting of the Mississippi Valley Medical Society will be held at the Pere Marquette Hotel, Peoria, Ill., September 27 and 28.

Scientific exhibits will be a feature of the meeting.

The officers recently elected are president, Dr C Paul White, Kewanee, Ill., president elect, Dr Grayson L Carroll, St Louis, first vice president, Dr Milton E Bitter, Quincy, Ill., second vice president, Dr E A Cunningham, Louisiana, Mo., third vice president, Dr Con R Harken, Osceola, Iowa, secretary-treasurer, Dr Harold Swanberg, Quincy, Ill. The members of the Board of Directors are from Illinois, Drs Charles Harmon (Springfield), G A Sihler Jr (Litchfield), L H Sloan and C C Maher (Chicago), E F Parker (Moline), E E Nystrom (Peoria) and Ralph McReynolds (Quincy), from Missouri, Drs F J Tainter and Clyde Dyer (St Louis), and W F Francka (Hannibal), from Iowa, Drs F A Hennessy (Calmar), J H Randall (Iowa City) and B J Dierker (Fort Madison).

The society has established an endowment fund, which is already a going affair, with a \$500 appropriation. All contributions to the fund will be invested in war bonds. A new plan for life membership, whereby the fee paid will depend on the applicant's age, has been adopted, and new, attractive certificates of life membership have been authorized. All fees for life memberships will be placed in the endowment fund, and hence in war bonds.

The January issue of the *Mississippi Valley Medical Journal*, called the "Chicago Number," contains some of the contributions by physicians of Chicago which were presented at the meeting of the society held in Quincy, Ill., last year. The rest of the papers will appear in the April issue, which will be called the "War Medicine Number" and will feature a symposium on war medicine.

## Correspondence

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### CLINICAL SIGNIFICANCE OF GLYCOGEN CONTENT OF LIVER

*To the Editor* —In order to prevent an erroneous impression, I wish to draw attention to some pertinent omissions from a paper by Dr Morton Korenberg entitled "Clinical Significance of Glycogen Content of Liver" in the December issue (ARCH INT MED 72:746 1943)

The studies which provided the data presented in this paper were made in the May Institute for Medical Research, the University of Cincinnati, and the Research Foundation of the Children's Hospital, Cincinnati. These studies were performed by Dr Waldo E Nelson, Dr Norton Nelson and me. Dr Korenberg, serving in the capacity of an intern, participated in some of the clinical studies and was recognized for this work as a junior author of a report entitled "The Hepatic Glycogen Reserves in Diabetes Mellitus" (*Endocrinology* 28:358, 1941). Subsequently, studies by E Perry McCullough and his co-workers utilized the phlorhizin procedure as presented in the aforementioned report.

Many of the data, comments and interpretations which appear in Dr Korenberg's paper were previously presented in the aforementioned report and in lectures to which Dr Korenberg had access. The remainder of the data which are presented in his paper were made available to him three years ago, when he prepared a thesis for a graduate degree. Permission to publish these data was neither requested nor granted.

No reference to these facts exists in Dr Korenberg's paper, an omission which makes it necessary for me to draw attention to the institutions in which the work was done and the investigators who did it.

MAJOR I ARTHUR MIRSKY, MC,

Army of the United States

The May Institute for Medical Research,  
Cincinnati (on leave of absence in military service)

### VALUE OF DETERMINATION OF UROBILIN

*To the Editor* —In the June 1943 number of the ARCHIVES OF INTERNAL MEDICINE, in the review of my book "La urobilina en el estado normal y patológico," it is said "The book, alas, definitely puts an end to the hopes of both investigator in clinical laboratories and clinician that urobilin, so tempting to test for, is of any practical clinical diagnostic value."

One of the more important conclusions at which I arrive in that discussion, however, is quite opposite to the reviewer's opinion. I definitely show that it has been proved by the experiments reported on that quantitative measuring of urobilin in urine or in blood (when present) is of considerable value for estimation of hepatic function. Quantitative determination of urobilin in bile is of distinct importance in the diagnosis of cholecystitis, and its measurement in feces is undoubtedly beneficial in certain special cases.

MARCELLO ROYER, M D, Buenos Aires, Argentina

## Book Reviews

Publicaciones del Centro de Investigaciones Tisiológicas, Hospital Tornu, Buenos Aires, Argentina Volume VI, 1943

The sixth volume of the research studies of the Center of Investigation of the Tornu Hospital, under the direction of Prof Roque A. Izzo, reflects a high caliber of work. Although it is essentially the product of a tuberculosis organization, including a painstaking hematometric study on normal and on tuberculous subjects by Mora and various pathologic studies of tuberculosis, cancer and miscellaneous topics by other members of the staff, the studies on the vitamin B complex by Costoya are outstanding in extent and thoroughness. After a painstaking review of the history, discovery, chemical constitution, preparation, pharmacology and standardization of the complex, the author focuses attention on methods of analysis and their practical application.

Although many principles have been used in analysis for vitamin B, the author was able to use the fluorescence produced by thiochrome developed from thiamine in blood and urine as a means of determining it. The readings were made in a Pulfrich photometer with an ultra-violet source of light. In a series of cases there were found averages of 15.04 and 31.66 micrograms per hundred cubic centimeters of blood and of urine respectively.

The studies on the vitamin B complex will be useful to biochemists, research workers, clinicians and clinical pathologists. The other reports are more for pathologists or persons engaged in research in tuberculosis.

The binding is heavy paper, the illustrations are good, and the paper, printing and type are excellent.

**A Hundred Years of Medicine** By C. D. Haagensen and Wyndham E. B. Lloyd Price, \$3.75 Pp 443, with 42 illustrations New York Sheridan House, 1943

This is an interesting bit of light reading that will serve to pass the time of the physician if he can find any idle moments these days. It is not a serious attempt to publish a history of medicine. The authors have given a short synopsis of medicine up to a hundred years ago. Then they have selected what appear to them to be the important advances during the past hundred years in medicine and surgery and in the social aspects of medicine. The nurses have not been entirely neglected. One might quibble a bit about the complete accuracy of some of the statements, and one might also raise a question about the wisdom of the selection of material in some instances. If either of these objections is valid, they constitute a reason for not putting this material before the lay reader. The material is rather technical for the lay reader to understand well. However, he must be greatly confused by much of the material that is directed at him in these days, and a little additional confusion will not do him irreparable harm. The jacket that surrounds the book states that both authors are physicians. According to this source of information Dr. Haagensen is a surgeon and pathologist on the faculty of Columbia University's School of Medicine and Dr. Lloyd is a specialist in public health working in England.

**Synopsis of Tropical Medicine** By Sir Philip Manson-Bahr, M.D., Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine Price \$2.50 Pp xii + 224, with 5 plates Baltimore Williams & Wilkins Company, 1943

The author states that this small volume was written in response to numerous requests to provide a guide to tropical medicine in a condensed form, suitable for medical officers and others whom the exigencies of the moment call to the tropics. It is of proper size to fit into one's pocket, and everything that it says is condensed in similar fashion.

The tropical diseases have been grouped under their causes: protozoal diseases, rickettsial diseases, bacterial diseases, virus diseases, fungous diseases, nutritional diseases, etc. Each disease is discussed according to much the same pattern—its cause, pathologic picture, clinical features, diagnosis, treatment and prevention. The whole story is told in a few lines. At the end is an excellent index, so that the perplexed physician can readily look up anything from A. L. 63 (if he wishes a preventive powder against lice) to zygote (if he is concerned with malaria).

It is remarkable to find such a complete handbook in such small compass. The author says that it represents, on his part, a small contribution to the war effort. Many physicians and students will be grateful to him for making it.

**Borderlands of Psychiatry** By Stanley Cobb, M D Price \$2.50 Pp 166 Cambridge Mass Harvard University Press, 1943

This little brochure represents a series of essays on subjects that have special interest to the author, to quote the introduction Cobb has prepared a splendid summary, it might be called, of many features of psychiatry that touch on the practice of every physician. The material represents special studies made by himself and others, it contains a certain number of illustrative case reports. Admixed with the scientific presentation there is a philosophic angle to Cobb's writing which adds much to the intellectual enjoyment of the material.

The essays are so well written and splendidly expressed that they make for easy reading while one is absorbing the psychosomatic point of view of the present day.

**The Arthropathies** By Alfred A de Lormier Price \$5.50 Pp 319, with 678 figures Chicago Year Book Publishers, Inc, 1943

This little book is really an atlas of the roentgenologic changes in the joints in various diseases. There are nearly seven hundred reproductions of films, illustrating all phases of the subject, together with concise descriptive notes. Unfortunately, some of the reproductions do not show up too well, and others are marred by the extraordinary method used to point out the lesions, which covers the cuts with letters and zigzag arrows. Figure 311 is a good example.

**The Dysenteric Disorders** By Sir Philip Manson-Bahr, M D, Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, with an appendix by W John Muggleton, M S M Second edition Price \$10 Pp vi + 629 with 23 plates and 108 figures Baltimore Williams & Wilkins Company, 1943

The first edition of this book was reviewed shortly after its appearance in 1939 (*J A M A* 114 1010 [March 16] 1940). It was regarded as a comprehensive description of the result of the author's experience in the tropics and his extensive practice in the Hospital for Tropical Diseases in London.

The second edition is much like the first. It is readable and has a fine bibliography. Medical officers and students will find it a particularly useful handbook, which gathers together current knowledge of the dysenteric disorders in a pleasant and instructive manner.

**A Synopsis of Clinical Syphilis** By James Kirby Howles, M D, M M S, Professor of Dermatology and Syphilology and Director of the Department, Louisiana State University School of Medicine Price, buckram, \$6.00 Pp 671, with index, illustrated St Louis C V Mosby Company, 1943

Section I of the book is devoted to general considerations of etiology, pathology, classification, symptomatology, diagnosis and treatment, section II, to systemic and regional syphilis and the final section, to problems of the familial and public health aspects of the disease. The appendix comprises historical notes on the condition. There is also a comprehensive bibliography alphabetically arranged.

The work is well organized, moderately condensed and well presented. There are numerous well selected illustrations. The reviewer has no hesitancy in recommending this book to students and practitioners of medicine.

**Your Arthritis What You Can Do About It** By Alfred E Phelps, M D Price, cloth \$2.00 Pp 192, with index, illustrated New York William Morrow and Company, 1943

This book was written for the laity with a twofold purpose—to tell the arthritic patient how best to cooperate with his own physician during treatment and to relieve his physician from the arduous, time-consuming task of giving detailed instructions concerning all the little things the patient can do to get the most out of life with the limitations imposed by the disease.

The views expressed represent the consensus of the leading rheumatologists in this country. There are no misstatements of fact, and the purpose of the work is admirably carried out.

**Manometric Methods as Applied to the Measurement of Cell Respiration and Other Problems** By Malcolm Dixon, with a foreword by Sir F G Hopkins Second edition Price \$1.75 Pp 157, with 20 figures New York The Macmillan Company, 1943

This book discusses in detail the technical aspects of apparatus and procedure used in measuring the rate at which an isolated tissue consumes oxygen and produces carbon dioxide. Although it is likely to interest the general reader as illustrating the high degree of refinement that has been attained in this field of scientific work, it is intended simply for use in research laboratories where the respiration of cells and tissues is being studied, the diagrams, tables and bibliography make it an excellent book for this purpose.

## PRIMARY ATYPICAL PNEUMONIA

REPORT OF ONE HUNDRED AND TWENTY-FIVE CASES, WITH AUTOPSY  
OBSERVATIONS IN ONE FATAL CASE

MAJOR ROBERT J. NEEDLES AND MAJOR PHILIP D. GILBERT  
MEDICAL CORPS, ARMY OF THE UNITED STATES

*They do certainly give very strange and new-fangled names to diseases—Plato*

An increasing number of reports in the literature indicates the presence of a pulmonary condition known by many names but called chiefly virus pneumonia or primary atypical pneumonia. Modern interest in the condition dates from the report of Bowen,<sup>1</sup> who called it acute influenza pneumonitis, feeling that it was a mild variant of pandemic influenza. In 1936, one year after Bowen's paper, Allen<sup>2</sup> reported 50 cases of the disease and emphasized, as had Bowen, the paucity of physical findings as compared with roentgen films of the chest. Beginning in 1938, Reimann, with various co-workers, has published a number of reports of the disease.<sup>3</sup> It has been Reimann's impression that the infection is caused by a filterable virus, though he admits the absence of conclusive proof. However, this work has served to emphasize the etiologic problem, and there is now a strong feeling that in many of the cases of pneumonia of nonbacterial origin there is a unity of the clinical and the pathologic picture.<sup>4</sup> Most writers agree that the disease is

not a new one, but evidence is at hand to show that its incidence is increasing. Thus Smiley and his group,<sup>5</sup> in a carefully controlled study, noted the appearance of the condition in 1937, with increasing numbers of cases in succeeding years. Goodrich and Bradford,<sup>6</sup> under conditions which insured complete clinical and roentgen examination of all patients with respiratory diseases, noted a definite increase in incidence of the disease between 1938 and 1940. That the condition has existed previously is emphasized by a recent publication from the United States Army which points out that 3 cases of pneumonitis represented in the Army Medical Museum dating from the American Civil War show a pathologic picture indistinguishable from that of the present infection. In the discussion of a paper by Reimann and Stokes<sup>3d</sup> read before the Association of American Physicians in 1939, Dochez, Cole and Libman united in stating that atypical pneumonia is not a new disease. In the Station Hospital at Hunter Field, in the period from January to December 1942, primary atypical pneumonia was found in 125 cases. In the ensuing two months an additional 25 cases were observed, making a total of 150 cases. This paper is a study of the disease as we have observed it, with analyses based on the first 125 cases. There was 1 fatality in the group, and autopsy observations will be presented in detail.

### REPORT OF CASES

CASE 1—*Primary atypical pneumonia of moderate severity* (fig 1)

A 24 year old white man had been entirely well until the day before his admission to the hospital. At that time he noted gradual onset of malaise, transient chilly sensations, generalized aching, anorexia and a nonproductive cough. There had been no preceding infection of the respiratory tract. He said he had not had shaking chills, pain in the chest or stained sputum. On his admission to the hospital his tem-

From the Medical and the Roentgenological Service, Station Hospital, Hunter Field, Savannah, Ga.

1 Bowen, A. Acute Influenza Pneumonitis, *Am J Roentgenol* **35** 168 (Aug) 1935.

2 Allen, W. H. Acute Pneumonitis, *Ann Int Med* **10** 441 (Oct) 1936.

3 (a) Reimann, H. A. An Acute Infection of the Respiratory Tract with Atypical Pneumonia, *J A M A* **111** 2377 (Dec 24) 1938. (b) Reimann, H. A., and Havens, W. P. An Epidemic Disease of the Respiratory Tract, *Arch Int Med* **65** 138 (Jan) 1940. (c) Kornblum, K., and Reimann, H. A. Roentgenological Aspects of Epidemic of Acute Respiratory Tract Infection, *Am J Roentgenol* **44** 333 (Sept) 1940. (d) Reimann, H. A., and Stokes, J., Jr. Epidemic Infection of the Respiratory Tract in 1938-1939. A Newly Recognized Entity, *Tr A Am Physicians* **54** 123, 1939. (e) Reimann, H. A. Infectious Diseases. A Review of Significant Publications in 1941-1942, *Arch Int Med* **70** 132 (July) 1942.

4 (a) Favour, C. B. Ornithosis (Psittacosis). A Report of Three Cases and a Historical Clinical and Laboratory Comparison with Human Atypical (Virus) Pneumonia, *Am J M Sc* **205** 162 (Feb) 1943. (b) Reimann H.

5 Smiley, D. F., Showacre, E. C., Lee, W. F., and Ferris, H. W. Acute Interstitial Pneumonitis. New Disease Entity, *J A M A* **112** 1901 (May 13) 1939.

6 Goodrich, B. C., and Bradford, H. A. The Recognition of Virus Type Pneumonia, *Am J M Sc* **204** 163 (Aug) 1942.

perature was 103 F, his pulse rate 100 and his respiratory rate 22. He did not appear severely ill. Aside from the elevation in temperature there were no abnormal findings, physical or laboratory. Studies of the sputum were attempted, but no significant organisms were found. Roentgen examination of the chest revealed early infiltration in the left pulmonary field, extending from the hilus midway into the parenchyma on that side.

His course in the hospital was not unusual for the disease. The temperature ranged from 101 F to a

charged from the hospital after an illness lasting five weeks and has remained well since.

CASE 2—Primary atypical pneumonia with fatal termination (fig 2)

A white man aged 23 was admitted to the station hospital on Nov 27, 1942. On admission, he stated that he had had a slight infection of the upper respiratory tract associated with headache for the past week. There had been a moderate amount of chilliness, malaise and anorexia. These symptoms had increased greatly in the twenty-four hours preceding the patient's admis-

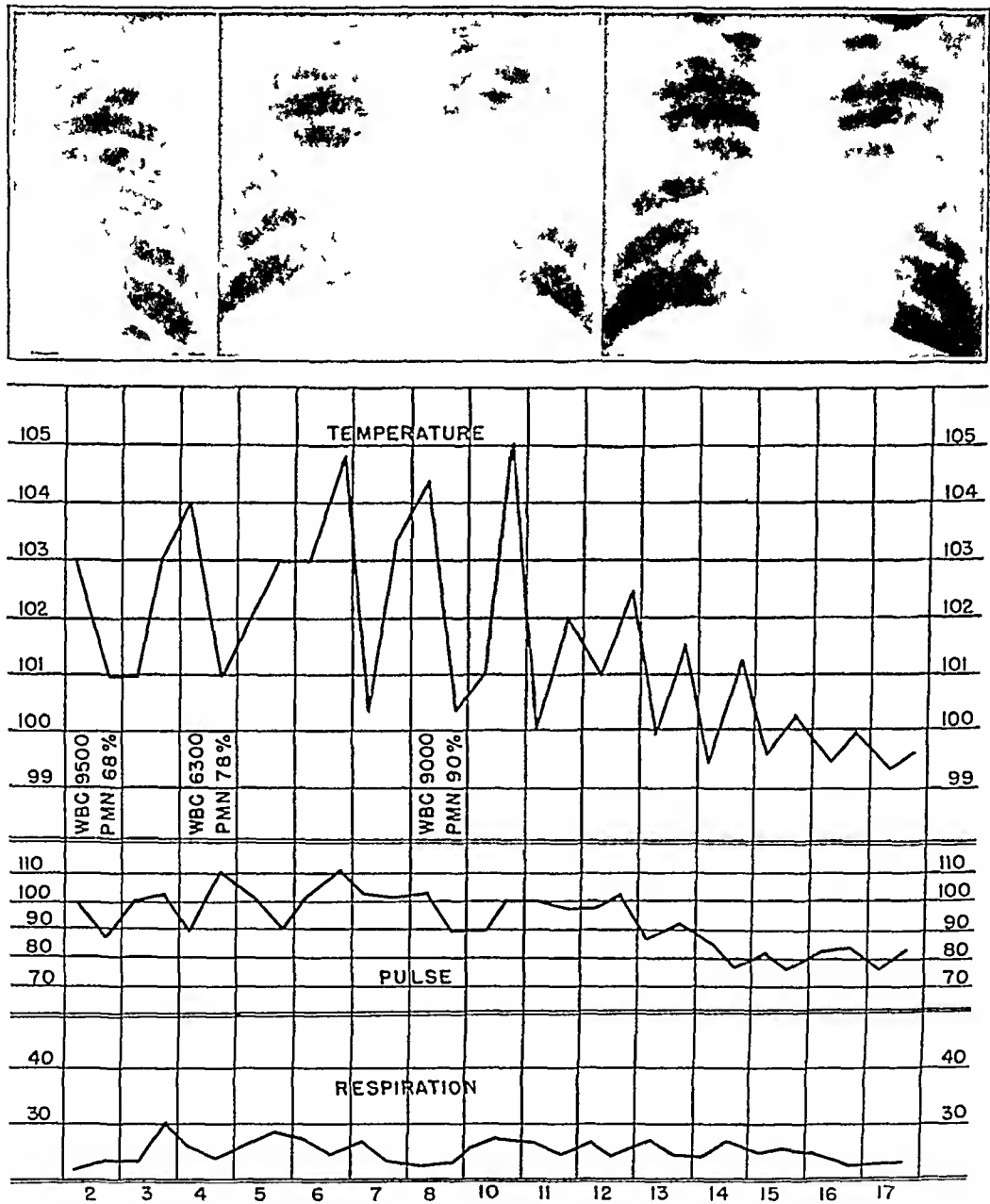


Fig 1—Clinical and laboratory data for case 1

high of 105 F for about one week, after which it fell gradually to normal after an illness of twenty-one days. The roentgenograms of the chest show the increasing involvement of the pulmonary fields, even after the patient was much improved clinically. Physical signs in the chest were limited to slight impairment of response to percussion over the involved areas, with scattered medium-sized rales as the patient improved. There was at no time a great deal of sputum. What was produced was mucopurulent and rather viscid. Relative bradycardia was noted, and the respiratory rate was not greatly elevated. The patient was dis-

charged from the hospital after an illness lasting five weeks and has remained well since. The initial temperature was 99.8 F, the pulse rate 88 and the respiratory rate 20. He did not appear seriously ill, and on examination no evidence of respiratory embarrassment was noted. There was slight reddening of the pharynx, without exudate. A slight hacking cough was noted, but only small amounts of mucoid material were expectorated. This was examined repeatedly by smear and by culture, but only a mixed growth of the usual oral flora was obtained. Tubercle bacilli could not be demonstrated. His course in the hospital was about as expected for this type of illness until the eleventh day. At that time there were

noted cyanosis, increased cough, still without sputum, and severe respiratory distress. The respiratory rate increased to 40 and later to 60 and 70. He was given supportive treatment, including use of an oxygen tent, transfusions of small amounts of blood and parenteral administration of fluids. No therapeutic measure prevailed, however. Cyanosis increased in spite of oxygen therapy, the chest appeared full of moist, sticky exudate, and he died on the eighteenth day of his illness. Death was apparently due to respiratory obstruction.

pink color of acute inflammation. The bronchial tree in both lungs was full of a creamy, viscid, yellow exudate, which was scraped away with some difficulty. This left a hemorrhagic bronchial mucous membrane, which in places seemed to be missing. Hemorrhagic phenomena were not noted in pleural or parenchymal structures. Swabs and cultures of the exudate as well as stab cultures of the lungs and of heart blood failed to show bacterial growth. By pressure on the cut lung, droplets of pus could be expressed from smaller and larger bronchiolar lumens throughout. On section

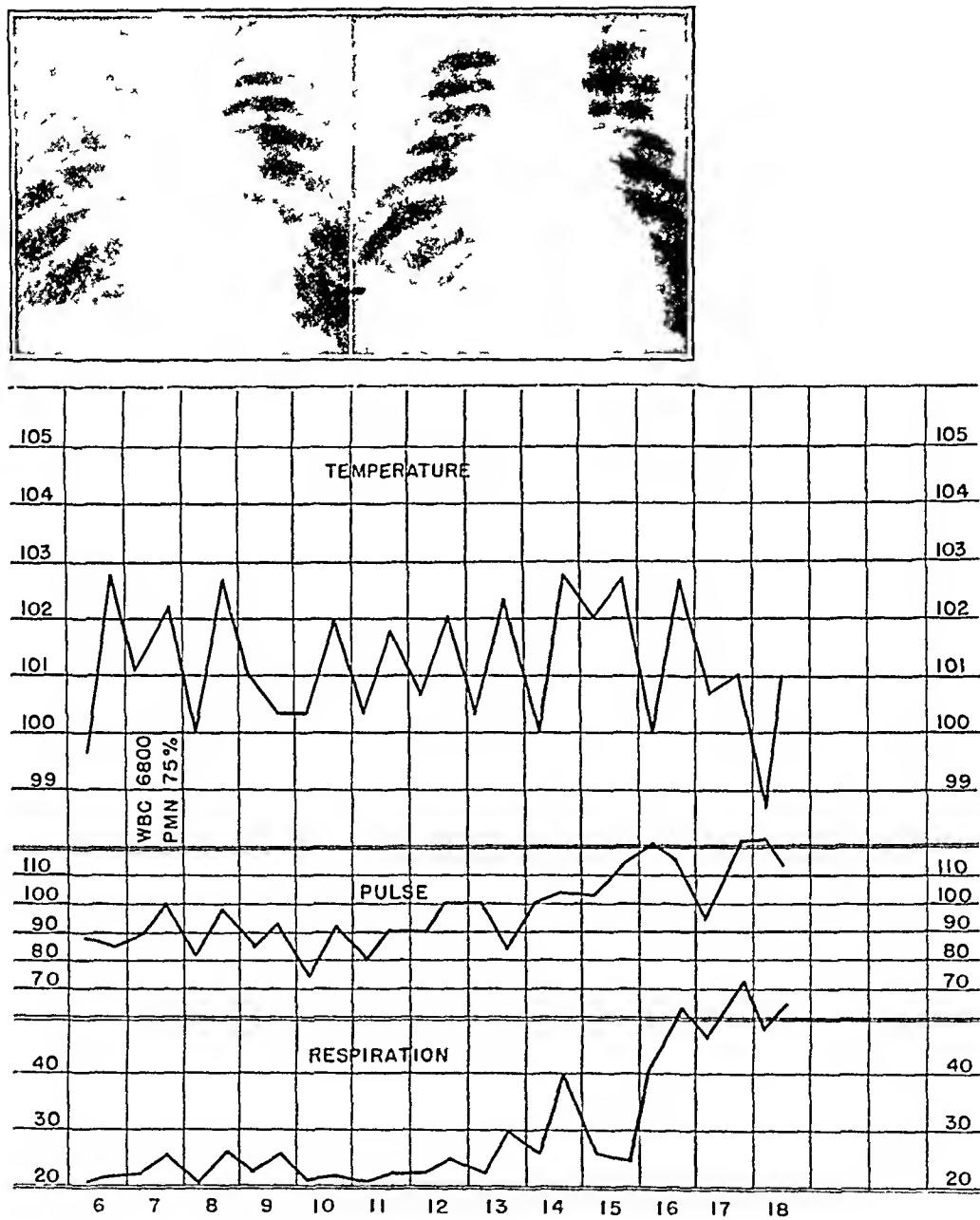


Fig 2—Clinical and laboratory data for case 2

*Gross Observations at Autopsy*—A complete post-mortem examination was carried out three hours after the patient's death. No significant changes were noted except in the lungs, and negative details are omitted. There was no excess of pleural fluid. The pleural surfaces appeared for the most part smooth and glistening and no gross fibrinous exudate was seen. The visceral pleural surfaces were light grayish pink. The lungs seemed to be increased in volume and did not collapse as the pleural space was opened. The pulmonary parenchyma had the feeling of a slightly moist sponge. No definite areas of consolidation could be felt and pieces of the lung floated in water. There was pronounced enlargement of the hilar nodes on both sides. These glands on section had the shiny, grayish

the lungs showed no gross or confluent areas of consolidation. For the most part the tissue was increased in consistency, as though there was increased fibrous tissue present, but changes typical of pneumonia were not seen except as noted. Scattered throughout both lungs, more prominent on the left, were hundreds of tiny, miliary-sized areas of infiltration, resembling very much the picture seen in miliary tuberculosis. These areas were grayish white and seemed to surround or be in close association with small bronchioles. The cut surface was grayish pink, and scattered everywhere throughout the lung were nodules, most of them about 1 mm in diameter resembling bronchiopneumonic consolidation. Grossly the picture was of increased pul-



monary resistance with milky pneumonitis and purulent bronchitis and bronchiolitis

*Microscopic Study*—The pleural surface showed scattered areas of polymorphonuclear exudate, with fibrin and round cell infiltration also noted. In the subpleural areas were numerous dilated blood vessels filled with red blood cells. In this area were large numbers of histiocytes, round cells and plasma cells. The pulmonary alveoli were in many areas elongated, tortuous and lined with a cuboidal epithelial membrane. The pattern as a whole was one of proliferation and exudation. The interstitial tissue was greatly thickened, the septums being packed with inflammatory cells of the round, wandering or plasma cell type.

#### COMMENT

*Onset and Clinical Course*—The majority of our patients had been conscious of ill health only one to three days before reporting at the hospital. This is somewhat less than the prodrome usually described. The initial symptom was somewhat variable, but as a group the symptoms were remarkably similar. It would be fair to say that the patient feels as if he were contracting a severe cold or influenza, and as far as we have been able to determine there is no real difference

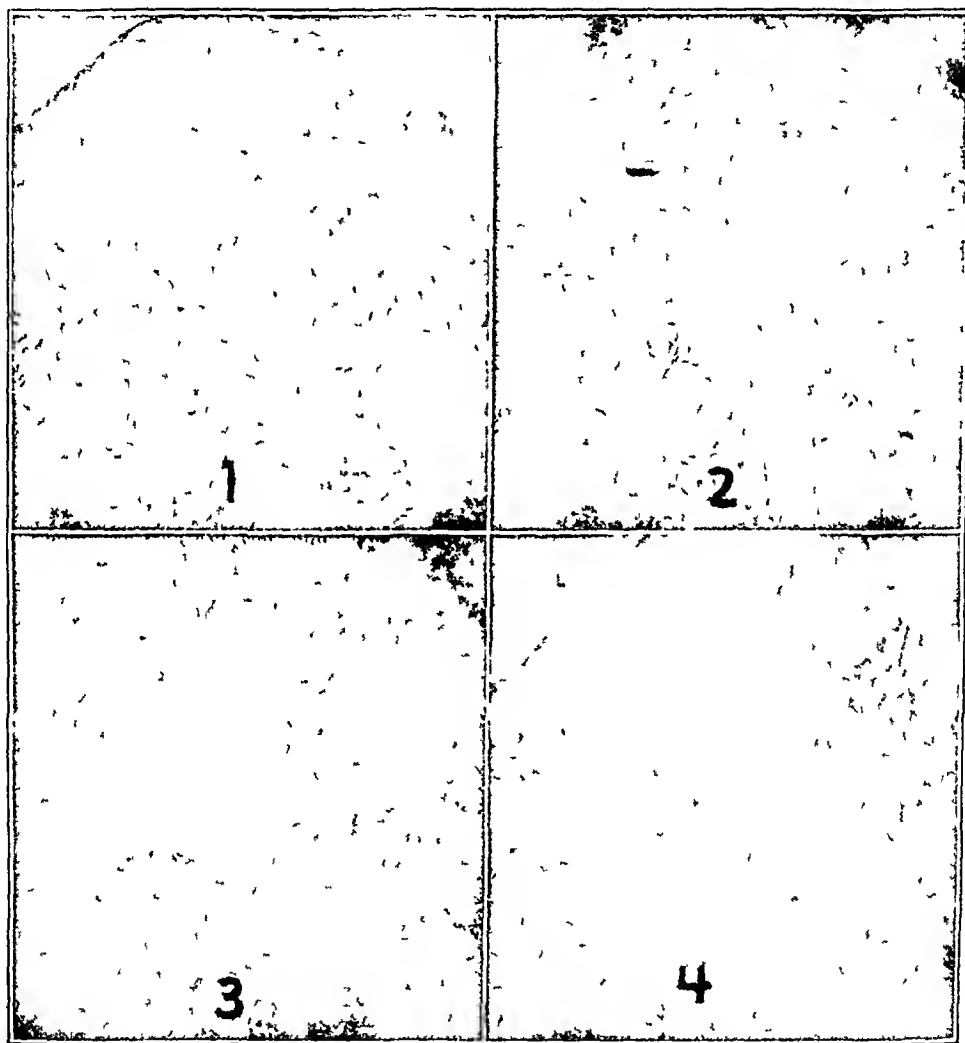


Fig 3 (case 1)—Section 1 shows an organizing pneumonic process in the parenchyma with engorgement of subpleural capillaries. A thin layer of fibrin and inflammatory cells is noted on the pleural surface. Section 2 shows a small bronchiole from which most of the lining epithelium has been lost. The lumen is filled with a polymorphonuclear exudate, and the surrounding parenchyma shows atelectasis and organizing pneumonitis. Section 3 shows a small bronchus filled with polymorphonuclear exudate. Section 4 shows emphysema and atelectasis in adjoining areas, and also thickening of the interalveolar septums and interstitial pneumonitis. (All magnifications are  $200\times$ )

Alveolar lining cells were cuboidal and often projected into the lumen. The bronchial lumens were universally filled with a purulent exudate, for the most part polymorphonuclear. Fibrin was not noted. There was scattered loss of bronchial mucous membrane, and in the areas of greatest involvement there was marked congestion of all vessels, but free blood was not seen. This picture, then, is one of interstitial pneumonia and purulent bronchitis (figs 3 and 4).

in the mode of onset of influenza and of atypical pneumonia. In figure 5 we have indicated the major presenting symptoms and their relative frequency. One of the most prominent early manifestations is malaise. The patient may state that for the past twenty-four to thirty-six hours he has not been definitely sick but has preferred

to remain quiet rather than assume his customary duties. The malaise increases, and with it may appear headache. The pain is general, and not more pronounced in the frontal than in the occipital region. It is a dull, gnawing pain and not associated with throbbing or with ocular manifestations. Sudden movements of the head do not tend to aggravate the pain. At the same time there will be sensations of chilliness. Shaking chills are uncommon, but even during warm weather the patient will state that he has been conscious of lowered body temperature. Loss of

often it is not prominent or the subject is not conscious of it at all. In the cases of more severe illness the cough is more prominent, but in the majority of cases even severe coughing is not productive of sputum in the first few days. With cough there is often a sensation of burning in the substernal region, aggravated by coughing and commonly felt to be due to tracheitis. Generalized aches and pains are common. The distress is muscular, and the joints are not involved. The pains are most common in the gastrocnemius-soleus groups of muscles and in

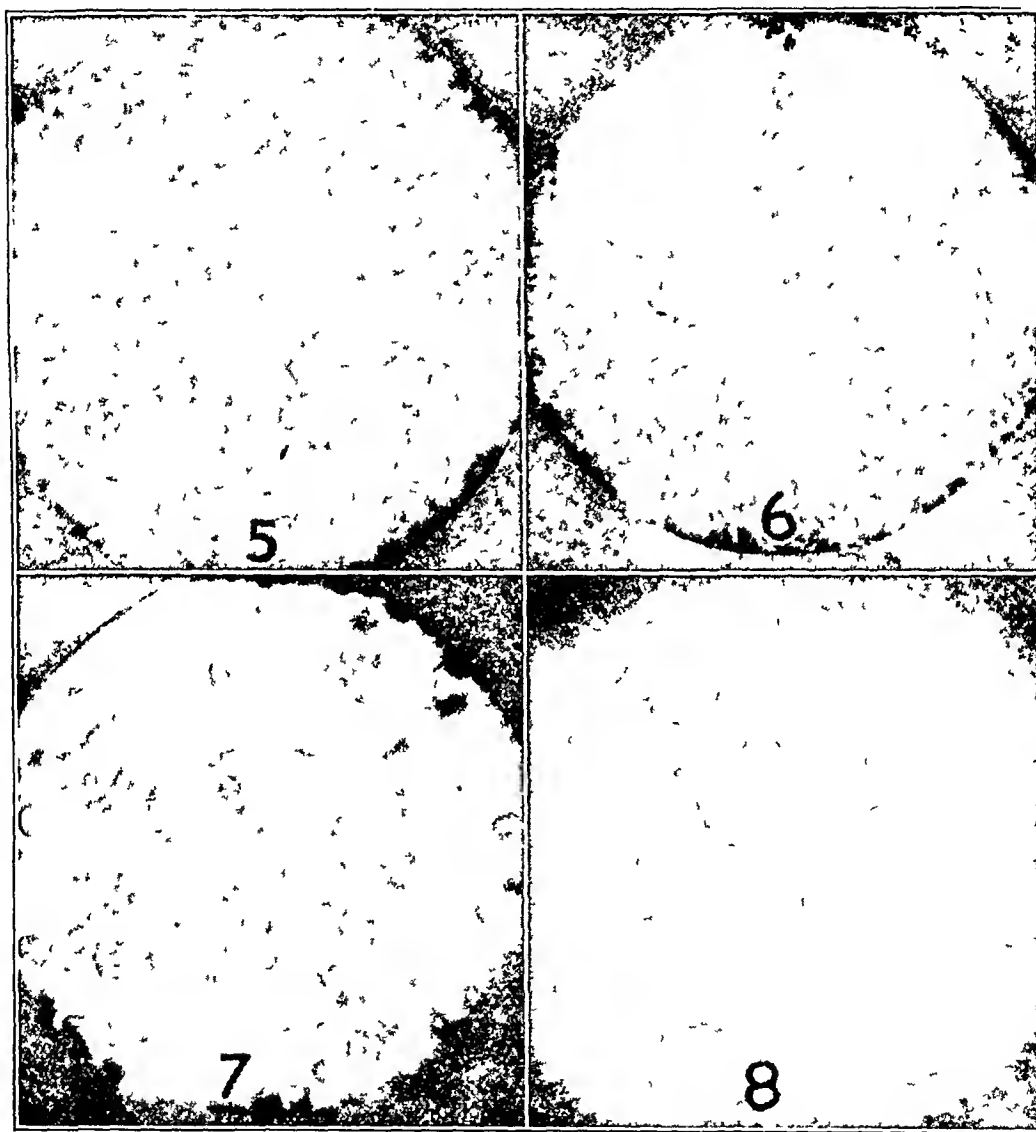


Fig. 4—Section 5 (400  $\times$ ), from a small bronchiole, shows papillary proliferation of the epithelium. Section 6 (400  $\times$ ), from a lung involved by interstitial pneumonia, shows pronounced thickening of the interalveolar septums, the cellular reaction here is predominantly mononuclear. Section 7 is an oil immersion view (900  $\times$ ) of an area shown in 6, the cells are monocytes, plasma cells and large mononuclear types resembling histiocytes. Section 8 (200  $\times$ ) is from an early milary abscess, the exudate is polymorphonuclear and there is loss of cell detail in some areas, indicating beginning necrosis.

appetite is common, though frank gastric revolt is rarely seen. Usually no food of note has been taken in the twenty-four hours previous to the patient's admission. We have not encountered abdominal pain, nausea or diarrhea. Symptoms referable to the nose and throat are not prominent. There may be slight rhinorrhea and minimal painful pharyngitis. Cervical adenopathy is not seen. Cough may occur early, but

the paraspinal masses. The pain is not associated with local tenderness but manipulation is moderately painful. As the disease progresses all symptoms are more severe, though in the mild attacks after three to six days the malaise recedes and the appetite returns. Headache is apt to persist longer. The cough usually increases in frequency and severity as the temperature approaches normal, and in about half the

cases it is eventually productive of viscid, light grayish yellow mucopurulent sputum. In severe attacks paroxysms of cough may be followed by some blood streaking of the sputum. We have not seen frank hemoptysis or rusty sputum. Epistaxis may occur in a few cases. Cyanosis is present in most of the moderately and severely

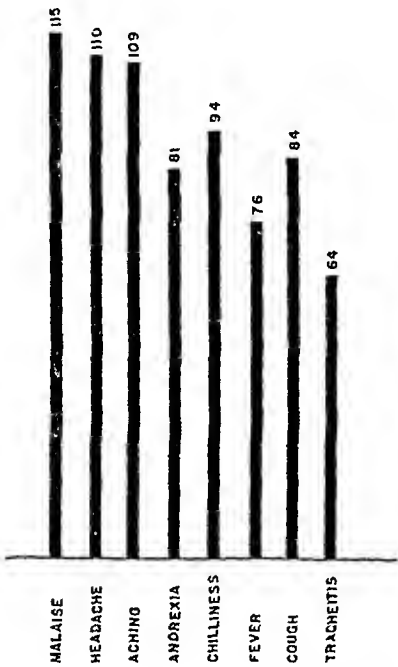


Fig 5—Relative frequency of the major presenting symptoms (125 cases)

ill patients. This is accompanied by dyspnea in a smaller number, though in most of our severely ill patients signs of respiratory difficulty were prominent enough to necessitate the use of oxygen. Herpes labialis is not common but occurred in 3 cases in this series. The febrile reaction is of remittent type, with the daily high level of temperature infrequently above 103 F. The usual patient with a moderately severe attack will have elevation of the temperature for seven to ten days, with gradual fall by lysis (fig 6). Relative bradycardia is noted in the attacks of only moderate or minimal severity. In seriously ill patients the pulse rate rises with the respiratory rate.

**Physical Signs**—Primary atypical pneumonia is not easily diagnosed without the aid of roentgen examination of the chest. After observing a large number of cases one is able to state with some degree of assurance that positive roentgen findings will be noted on the basis of history alone. However, it is constantly surprising to us to note how extensive the parenchymal involvement may be with minimal or no physical signs. Since, as we have pointed out, there is little to differentiate the disease from influenza, positive statements as to the presence or absence of pulmonary involvement may not be made without roentgen examination. In the case of

the patient but recently admitted to the hospital special attention should be given to comparative percussion of the pulmonary fields, since it is our feeling that the earliest changes are to be found in slight relative impairment over the involved areas of the lungs. This is often accompanied by slight diminution in the intensity of the transmitted breath tones. Changes in quality of the breath tones, such as bronchial and tubular breathing, were not a feature in this series of cases. Moisture in the bronchial tree as evidenced by the presence of rales is a late finding in most cases. The rales are usually of the moist type rarely being crepitant and in the absence of clinical evidence of bronchitis not being musical. In severe attacks, with large quantities of exudate filling the bronchial lumens, examination will show mucous rales over most of the pulmonary fields. The abdominal examination is not revealing, and enlargement of solid viscera is not seen. Abdominal distention, so common in severe lobar pneumonia, is absent in even critically ill patients suffering from primary atypical pneumonia.

**Röntgenologic Findings**—The earliest appearance of changes detectable in the roentgenograms of the chest in these cases is on the second

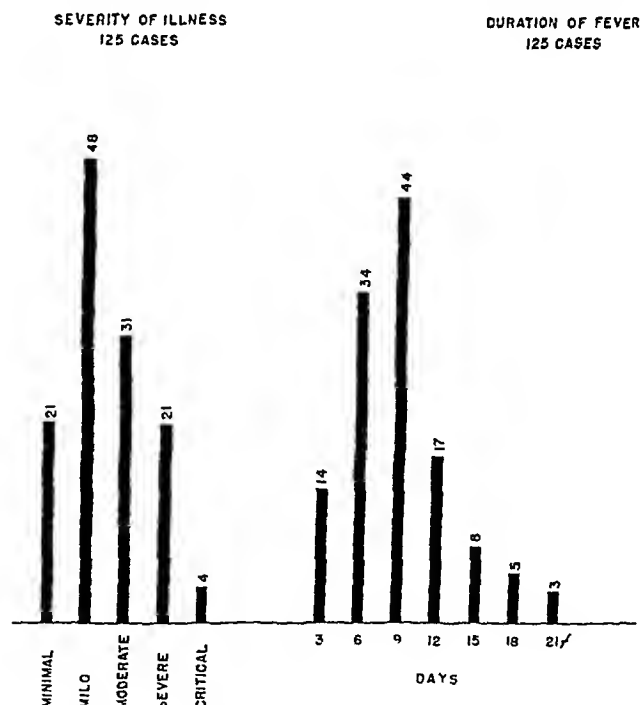


Fig 6—Relation of the severity of the illness to the duration of fever

or third day. The symptoms are usually in advance of the initial roentgen changes, just as in the later stages of the disease the roentgen changes are far in advance of changes in the clinical appearance of the patient. In several cases in which examinations were made in the first twenty-four hours of the illness no demon-

stable changes were noted, and serial films thereafter demonstrated the gradual development of the pulmonary involvement. Thus we found that the first changes take the form of a faint and usually localized exaggeration of the peribronchial markings, so that they have a streaked or linear appearance. The hilar markings are usually prominent, and the changes may

ordinarily extend beyond the middle of the lung, and may cling closely to the lower mediastinal border. The subsequent changes are extensions of the early picture. The markings increase in prominence, and the area exhibits a mottled, seldom homogeneous increase in density. Frank and clearcut shadows, such as are present with lobar pneumonia, are seldom seen. Pleural

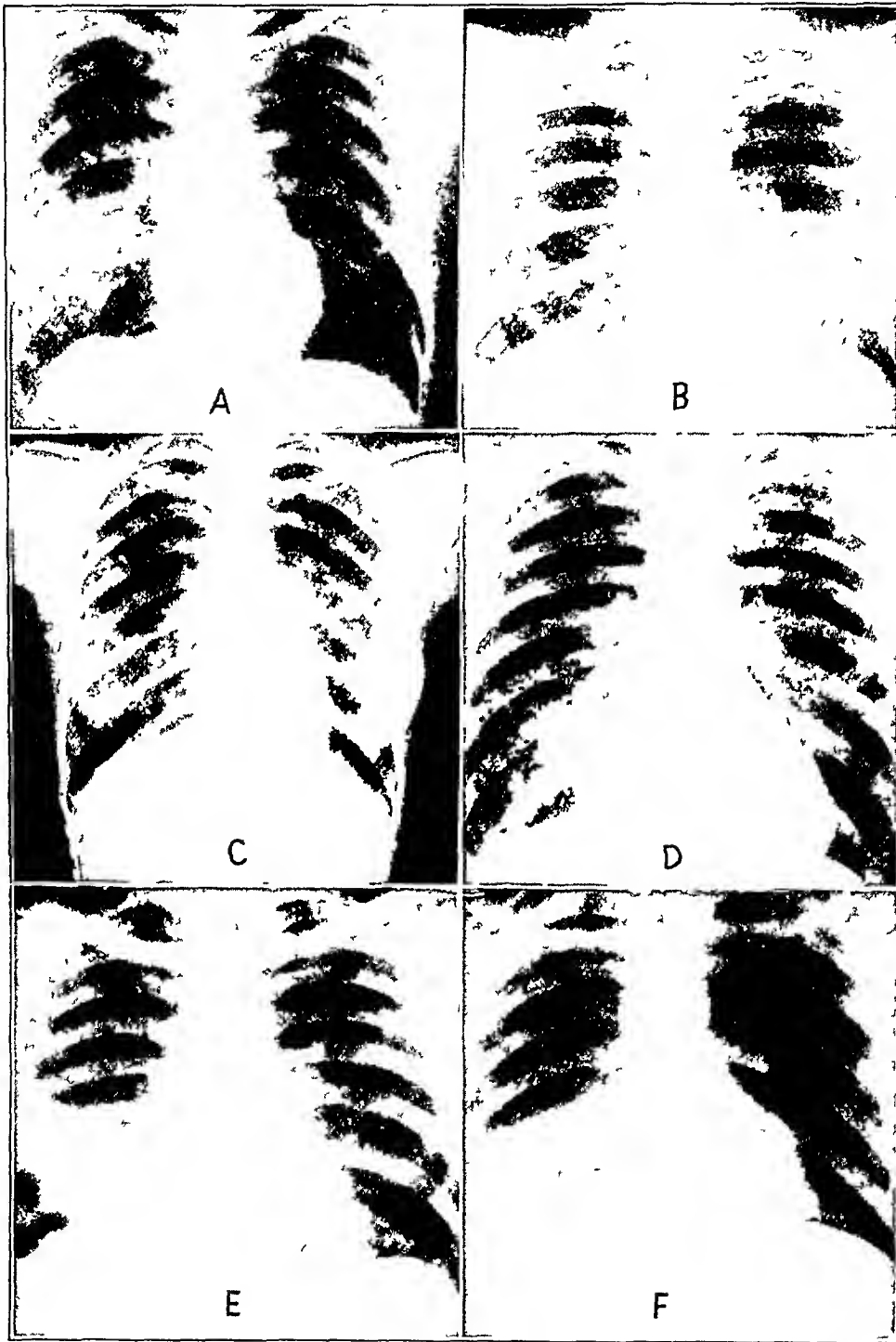


Fig. 7—Roentgenograms for patients with mild primary atypical pneumonia. None of the patients was seriously ill. Patient B was afebrile when the film shown was taken. Patient C had an illness that resembled primary tuberculosis.

be projected into the pulmonary fields from one or both hilar regions. There seems to be no preference for one lung over the other, but the disease more commonly affects the lower pulmonary fields. The mild attacks are usually unilateral, and the more severe ones are generally bilateral. The earliest changes do not

thicken or evidence of pleural exudate is rare, having occurred in but 1 case in this series. In the most severely ill patients, those having marked dyspnea, cyanosis and large amounts of sputum, roentgen examination reveals a diffuse, mottled infiltration resembling miliary tuberculosis. In 1 case in the series it was difficult

to distinguish the lesion from that of a primary tuberculosis complex. In another case in which the lesion was in the left upper pulmonary field, finding of tubercle bacilli finally differentiated this condition. In many cases there is little to choose in the roentgen picture between primary atypical pneumonia and variants of the fungous infections or pneumoconiosis (figs 7 and 8)

tubercle bacilli, fungi and yeasts. From the data accumulated it is apparent that there is no single bacterial pattern in the disease. Most of the cultures of sputum showed a mixed growth consisting of *Micrococcus catarrhalis*, nonhemolytic streptococci and occasional pneumococci of the higher groups. *Haemophilus influenzae* was not found in any case. Virus studies were not

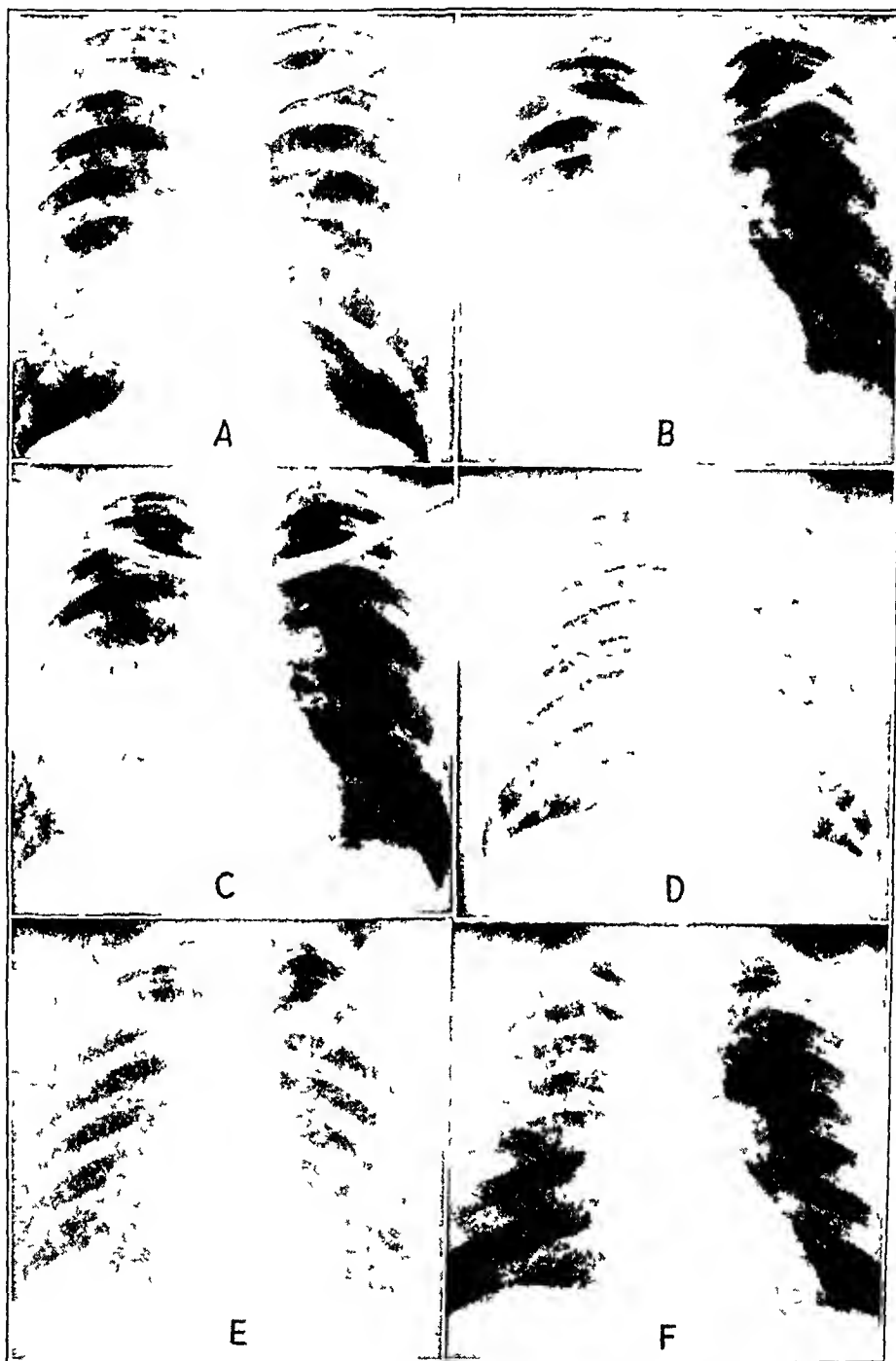


Fig 8—Roentgenograms for patients with severe primary atypical pneumonia. Patients *B* and *E* were seriously ill. All the patients recovered.

*Laboratory Data*—Examinations of the sputum have been done one to many times in all of our cases. These have included search for predominating organisms by culture, attempts to find typable pneumococci and also search in selected cases for other organisms, such as

carried out. The leukocyte response is shown in figure 9. It will be noted that in most of the cases the values were in the normal or slightly above normal group. In rare instances the count was above 15,000. The differential leukocyte study was not revealing, percentages of poly-

morphonuclear cells being between 65 and 80, with small lymphocytes and monocytes in their customary ratio. No abnormality of other elements was noted, and in summarizing it is fair to say that the white blood cell count in these cases is of no help or significance except by its almost complete absence of pathologic intensity. In the urine of severely ill patients it was common to find a trace of albumin, but no other changes were noted. Agglutination tests against the usual gram-negative organisms were made in a few cases, with negative results. Complement fixation tests for various strains of Rickettsia or other exotic organisms were not done. Blood cultures were made in all of the early cases, but no positive result was obtained.

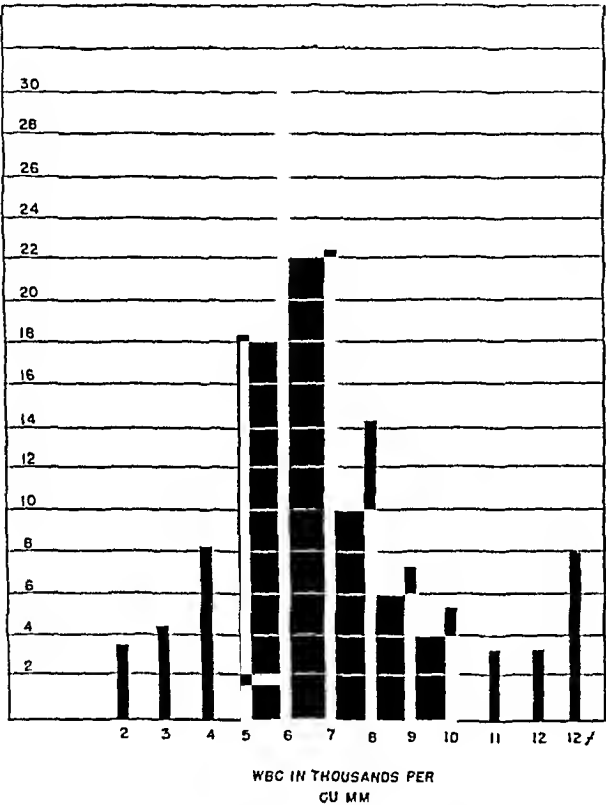


Fig 9—Leukocyte response (125 cases)

TREATMENT

Most patients with primary atypical pneumonia recover without any medication at all. Rest in bed, adequate ingestion of fluids and attention to elimination seem to be sufficient for the mildly ill patients, and recourse to various special forms of treatment is not necessary. It is necessary to avoid inadequately deliberated methods, since the origin of the condition is obscure and the object of treatment should be to assist the normal combative forces of the body. Thus it has not seemed necessary to use large amounts of salicylates, sodium bicarbonate or other agents designed to relieve the patient's discomfort. An occasional small dose of codeine may be helpful in combating headache. When indicated, the use

of expectorants, such as ammonium chloride, may be beneficial in aiding the patient to raise and rid himself of the mucoid material clogging the bronchial tree. Inhalations of warm steam treated with benzoin, menthol or some other inhalant may be comforting. We have found the use of finely atomized solutions of 1:100 epinephrine hydrochloride and neo-synephrine hydrochloride, as recommended by Barach,<sup>7</sup> helpful, and we believe that his suggestion of some type of positive pressure administration of oxygen is good. We have used oxygen by tent or by mask for all of our seriously ill patients, and there seems to be no doubt that it is a life-saving measure for such patients. Another measure which may be helpful is the use of inhalations of pure carbon dioxide as described by Gunther and Blond.<sup>8</sup> The hyperventilation induced by this procedure, followed usually by a paroxysm of coughing with production of large amounts of sputum, often serves to clear the bronchial tract for several hours. Careful watch must be kept for the onset of symptoms of increased severity. A rising respiratory rate and increased cyanosis are indications for prompt and energetic treatment. The use of sulfonamide compounds is not helpful. As previously indicated by one of us,<sup>9</sup> drugs of this group have no effect on the course of primary atypical pneumonia. Repeated statements to this effect are to be found in the literature and require no elaboration. For a critically ill patient the introduction of a powerful drug may actually handicap his chances for recovery. Transfusions of small amounts of whole blood, 250 cc being given on alternate days, are possibly of some benefit for seriously ill patients. If available, use of donors who have recovered from the disease is advised, although positive evidence is lacking that immune bodies exist in such blood. Fluids should be given parenterally whenever intake by mouth is insufficient.

COMMENT

Certain features of this disease are of more than ordinary interest. Among these is the close resemblance both clinically and pathologically to some types of influenzal pneumonia. As de-

7 Barach, A. L. Physiologically Directed Therapy in Pneumonia, *Ann Int Med* 17:812 (Nov.) 1942.  
Barach, A. L., and Molomut, N. An Oxygen Mask Metered for Positive Pressure, *ibid* 17:820 (Nov.) 1942.  
8 Gunther, L., and Blond, H. H. Observations on the Use of Carbon Dioxide in Early Pneumonia. *Am J M Sc* 193:525 (April) 1937.  
9 Needles, R. J. Atypical Pneumonia. *Internat Clin* 4:84 (Dec) 1940.

scribed by many writers<sup>10</sup> during and after the great pandemic of influenza in 1918-1919, there is little difference between the pulmonary changes in that disease and those in our case in which autopsy was done. These include a primary interstitial pneumonia with severe capillary bronchitis. The character of the disease may change during an epidemic, as pointed out by Boyd,<sup>11</sup> who stated

One of the most extraordinary features of influenza is the way it changes its character when it takes on pandemic form. For years it appears as the mildest of diseases, attacking a person here and there, but with a negligible mortality. Suddenly, with hardly a warning, it sweeps across the world like "a blast from the stars" and kills millions of persons in a short time.

We have been unable to connect this disease with influenza by means of virus studies, but that there is a close similarity in other ways no one can doubt. The physical findings support

10 MacCallum, W. G. Pathology of the Pneumonia Following Influenza, *J. A. M. A.* 72:720 (March 8) 1919. Jordan, E. O. Influenza Epidemic of 1918, *ibid.* 89:1603 (Nov. 5), 1689 (Nov. 12), 1779 (Nov. 19) 1927. Malloch, A., and Rhea, L. J. Fatal Bronchiolitis and Bronchopneumonia Caused by Bacillus Influenzae of Pfeiffer During an Inter-Pandemic Period, *Quart. J. Med.* 14:125 (Jan.) 1921. Opie, E. L. The Pathologic Anatomy of Influenza, *Arch. Path.* 5:285 (Feb.) 1928. Winternitz, M. C., Wason, I. M., and McNamara, F. P. The Pathology of Influenza, New Haven, Conn., Yale University Press, 1920. Opie, E. L., Blake, F. G., Small, J. C., and River, T. M. Epidemic Respiratory Disease, St. Louis, C. V. Mosby Company, 1921. Brannan, D., and Goodpasture, E. W. The Pathology of Pneumonia Caused by Bacillus Influenzae During an Interepidemic Period, *Arch. Int. Med.* 34:739 (Dec.) 1924. Wolbach, S. B. Pathology and Bacteriology of Fatal Influenza, *Bull. Johns Hopkins Hosp.* 30:104 (April) 1919. Rivers, T. M., Benjamin, B., and Berry, G. P. Psittacosis. Report of a Case, *J. A. M. A.* 95:577 (Aug. 23) 1930. Klotz, O. Studies on Epidemic Influenza, Pittsburgh, University of Pittsburgh School of Medicine, 1919, p. 207.

11 Boyd, W. The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1941, p. 155.

the thesis that the essential picture is one of interstitial pneumonitis. Thus in the early stages physical examination is apt to be fruitless, for most of the physical signs in the chest are dependent on fluid in the pulmonary parenchyma, pleural space or bronchial tree, and none of these are present in the early stages. Later, as the bronchial exudate becomes more prominent, physical signs increase in intensity. Another feature of interest is the lack of specific treatment. Thus it becomes necessary to exert unusual care not to minimize the disease because in its early stages it may appear benign. Changes in the respiratory rate and an increase in cyanosis are indications for the most active treatment, since the obstruction of the bronchial tree by large amounts of exudate vitiates attempts to provide adequate pulmonary aeration. Likewise, the interstitial nature of the pneumonitis interferes with transfer of oxygen to the circulating blood and makes the therapeutic problem more difficult. Early attack on symptoms of spreading infection is necessary.

#### CONCLUSIONS

There appears to be an increasing number of cases of an interstitial pneumonitis associated with capillary bronchitis, of undetermined cause, which has shown little tendency to excessive mortality.

Evidence indicates that the cause is to be found in the group of virus-Rickettsia agents which is also responsible for a wide variety of pulmonary infections of similar character.

Attention is called to the striking similarity of the symptoms and of the anatomic changes in this disease to those present in certain cases of influenzal pneumonia.

Treatment must remain symptomatic pending development of new therapeutic agents effective in combating virus infections.



# EFFECTS OF UNILATERAL NEPHRECTOMY IN TREATMENT OF HYPERTENSION

## AN EVALUATION

WILLIS SENSENBACH, M D

WINSTON-SALEM, N C

As a result of the experiments of Goldblatt<sup>1</sup> by which he demonstrates that hypertension can be produced in experimental animals by the application of a silver clamp to one or both renal arteries and of the publication of papers by Longcope<sup>2</sup> and Weiss and Parker<sup>3</sup> indicating the role of pyelonephritis in the pathogenesis of hypertension, a new approach to the treatment of hypertension in selected cases was gained, which at that time gave promise of considerable success. Physicians began to search especially for unilateral renal lesions in patients with elevated blood pressure in the hope of relieving the hypertension by removal of the affected kidney. Butler,<sup>4</sup> in 1937, was apparently the first to report a cure of hypertension by removal of a single pyelonephritic kidney. Since that time many reports have appeared in the literature concerning the treatment of hypertension by unilateral nephrectomy, and many more unreported cases of such treatment probably exist. On the other hand, little has been written about the cases in which nephrectomy has been done

and in which the elevation of blood pressure has remained unchanged. Furthermore, too many cases have been reported as instances of cure within a few weeks or months after operation, and hence lack adequate follow-up checks on the subsequent course of the blood pressure. Ayman<sup>5</sup> has stressed the fact that too frequently various therapeutic procedures have been given credit for apparently successful results in the reduction of blood pressure when these results have been in reality due to uncontrolled factors operating on the lability of the blood pressure and the hypertensive personality. One must be critical in evaluating changes in blood pressure following nephrectomy, or, for that matter, any surgical procedure, for a reduction in blood pressure to or toward a normal level is common after such procedures and even during prolonged rest in bed without surgical intervention. Such a fall in blood pressure may persist for some time, but most frequently it is temporary and the pressure gradually rises to its previous hypertensive level in a few weeks or months. Braasch<sup>6</sup> stated that it is necessary to follow patients who have had unilateral nephrectomy for hypertension for at least two years before they can be considered cured with any certainty. He states that of 198 hypertensive patients on whom various types of renal surgical operations were performed the hypertension was permanently relieved in 65. Seventeen patients had a post-operative drop in blood pressure but the hypertension returned in a few weeks or months, and in "several cases" the blood pressure remained normal for as long as two years and then returned to its preoperative level. He further states that the hypertension was relieved more often by nephrectomy than by other "more conservative" procedures.

From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College

Dr M C Bowman made the anatomic study of the kidneys in cases 1 and 2

Dr J R Williams gave me permission to report case 2

1 Goldblatt, H, Lynch, J, Hanzal, R F, and Summerville, W W. Studies on Experimental Hypertension. I The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J Exper Med* **59** 347, 1934. Goldblatt, H. Studies on Experimental Hypertension. V The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann Int Med* **11** 69, 1937, Experimental Hypertension Induced by Renal Ischemia, in *Harvey Lectures, 1937-1938*, Baltimore, Williams & Wilkins Company 1938, p 237

2 Longcope, W T, and Winkenwerder, W L. Clinical Features of Contracted Kidneys Due to Pyelonephritis, *Bull Johns Hopkins Hosp* **53** 225, 1933

3 Weiss, S, and Parker, F. Relation of Pyelonephritis and Other Urinary Tract Infections to Arterial Hypertension, *New England J Med* **223** 959, 1940

4 Butler, A M. Chronic Pyelonephritis and Arterial Hypertension, *J Clin Investigation* **16** 889, 1937

5 Ayman, D. An Evaluation of Therapeutic Results in Essential Hypertension. I The Interpretation of Symptomatic Relief, *J A M A* **95** 246 (July 26) 1930, II The Interpretation of Blood Pressure Reduction *ibid* **96** 2091 (June 20) 1931

6 Braasch, W F. Surgical Kidney as an Etiological Factor in Hypertension, *Canad M A J* **46** 9 1942

It is the purpose of this report to review some of the cases from the literature in which nephrectomy has been performed for hypertension, especially in regard to the incidence of actual cure following this procedure, and to report 4 cases, in 2 of which unilateral nephrectomy failed to lower the patient's blood pressure, in 1 of which nephrectomy not only failed to lower the blood pressure but resulted rather in a prompt rise in the blood pressure to levels well above the pre-operative range, and in 1 of which the blood pressure promptly fell to normal levels and has remained normal for over three and one-half years

#### REPORT OF CASES

**CASE 1**—V J, a 39 year old housewife, was feeling well until four days before admission to the hospital, when she awoke at night with severe frontal and temporal headache and pain in the left flank and left costovertebral angle. During the night the pain decreased in severity, but it persisted, and on the following day she consulted her physician, who told her that she had high blood pressure. Two days before admission she began having more intense frontal and temporal headache, and she noted stiffness and pain on motion of her neck. During the ensuing two days the pain in the costovertebral angle and flank almost completely subsided, and she entered the hospital complaining chiefly of headache and stiffness of the neck.

She gave a history that suggested that she had passed a renal calculus when she was a small child, but she had had no urinary symptoms since then except for nocturia, with urination two to three times a night, for the past ten years.

**Physical Examination**—On admission to the hospital the patient was drowsy and appeared to be acutely ill. The neck was slightly rigid, but the Kernig sign was negative. The pupils were equal and regular and reacted to light and in accommodation. The temporal margins of the optic disks were somewhat indistinct, but there was no definite papilledema. The retinal arterioles appeared to be normal, but the retinal veins were strikingly full. No hemorrhages or exudates were seen. The heart was slightly enlarged to the left. There were an apical systolic murmur and a faint presystolic gallop with accentuation of the first sound. The blood pressure was 180 systolic and 110 diastolic. The lungs were clear, and the cervical veins were not distended. The liver was not felt, and there was no edema of the extremities. There was slight tenderness at the left costovertebral angle. The lower pole of the right kidney was easily palpable and questionably enlarged. Neurologic examination gave negative results.

**Laboratory Findings**—Repeated examinations of the urinary sediment revealed a negative to 1 plus reaction for albumin, numerous white blood cells and occasional red blood cells. Colon bacilli were grown repeatedly from the catheterized urine. Examination of the blood revealed 3,740,000 red blood cells, 115 Gm of hemoglobin, 12,360 white blood cells and a normal differential count. The nonprotein nitrogen content of the blood was 25 mg per hundred cubic centimeters, the calcium content 9 mg and the phosphorus content 4.6 mg. Lumbar puncture revealed a clear fluid under normal pressure, with 1 cell and a negative Pandy reaction. The Kahn reactions of the blood and the spinal fluid were negative.

Roentgen examination of the chest showed evidence of healed tuberculosis at the apex of the left lung and a very small area of questionably active tuberculosis at the apex of the right lung. No sputum could be obtained, but examination of the gastric contents failed to reveal tubercle bacilli. Repeated roentgen examinations of the lungs showed no change in the lesion, and it was considered to be quiescent. Examination of the urine by direct smear and by guinea pig inoculation failed to reveal tubercle bacilli.

Because of the infection of the urinary tract the patient was given sulfacetimide and later sulfathiazole. In spite of this therapy the urine continued to show *Bacillus coli* on culture. Intravenous injection of phenol-sulfonphthalein on two occasions revealed 59 per cent and 50 per cent excretion of the dye in two hours. The maximal specific gravity of the urine was 1.017 (Fishberg technic). A roentgenogram of the abdomen revealed a large staghorn calculus in the left kidney. Retrograde pyelograms confirmed the presence of the staghorn calculus in the left kidney and revealed a marked hydronephrosis on that side. The right kidney appeared to be normal. Indigo carmine appeared in normal time and in good concentration on the right. On the left the dye appeared, but in very poor concentration. Urine drained from the left kidney three to

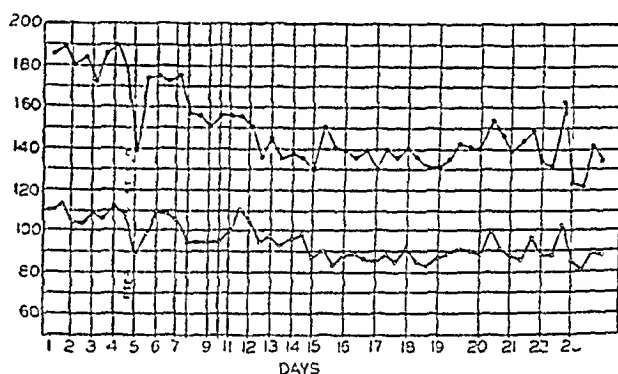


Chart 1 (case 1)—Effect of rest in bed on blood pressure

four times faster than from the right. Intravenously injected phenolsulfonphthalein appeared on the left side in five minutes and on the right side in six and one-half minutes. The urine from the left kidney grew hemolytic *Staphylococcus aureus*. The urine from the right kidney was sterile.

**Clinical Course**—The blood pressure on the patient's admission was 190 systolic, 110 diastolic. While she was at rest in bed, over a period of twenty-two days, the blood pressure gradually fell and became stabilized at a level of 140 systolic and 90 diastolic (fig 1).

After rather intensive treatment of the infection of the urinary tract with both sulfacetimide and sulfathiazole the urine became free of *B. coli* but remained infected with the hemolytic staphylococci. She was seen by a urologic consultant, who advised operation, the opinion being that the question of nephrectomy or nephrolithotomy should be decided after the kidney had been exposed. The operation was performed by Dr W E Woodruff. The kidney was found to be greatly enlarged but did not show gross evidence of perinephritic infection. Because of the patient's hypertension and because it was believed that removal of the three-dimensional calculus would result in excessive damage to the kidney, it was thought that nephrectomy rather than nephrolithotomy was the operation of choice, and the left kidney was removed.

*Gross and Microscopic Observations on the Kidney—*  
**Gross Description** The specimen consisted of the left kidney, which had been partially opened before reaching the laboratory. It weighed 162 Gm. The external capsular surface was smooth, and a small amount of perinephric fat was present. The capsule was not thickened and stripped fairly readily, although in certain areas it was adherent to the cortical surface. The cut surface of the kidney was brownish red. The cortex averaged 0.7 cm in thickness, and there was no evidence of distortion of the cortical markings. The medulla averaged

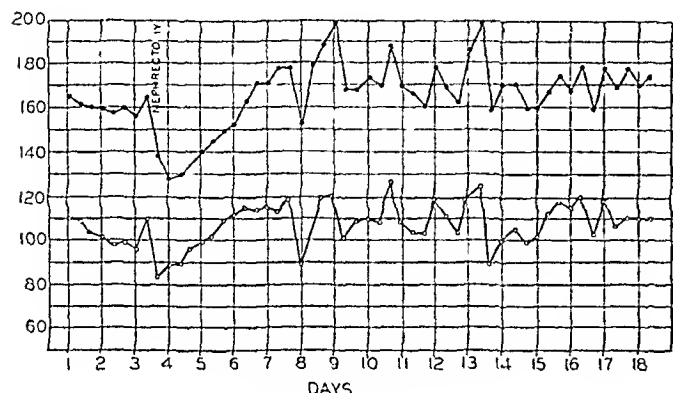


Chart 2 (case 1)—Blood pressure after nephrectomy

1.2 cm in thickness. The pelvis of the kidney was slightly dilated and was partially occupied by an irregular, faceted stone which measured 5 by 2 by 1 cm. The stone was light yellowish, and there were numerous projections into the calices, the largest projection being into the inferior major calix. The ureter came off in its usual position, and 6 cm of the superior portion of the attached ureter was included in the specimen. There was no evidence of ureteral dilatation.

**Microscopic Description** In the renal cortex an average of three glomeruli were observed per high power field. The glomerular capsular epithelium and the epithelium covering the capillary loops were thin and flat. The capsular spaces were empty except for an occasional one which contained a small amount of light pink-staining, homogeneous material. No inflammatory cells were observed within the renal corpuscles. The glomerular capillary loops were vascular, but an occasional small, partially fibrosed glomerulus was observed. There was no evidence of tubular degeneration. The arterioles and the small arteries appeared normal, but an occasional interlobular artery was seen in which there was some thickening of the media. The renal pelvis was lined with transitional epithelium beneath which there were chronic inflammatory cells. Scattered throughout the interstitial tissue of the medulla and cortex were focal groups of chronic inflammatory cells. These cells could also be seen in thin cords between the tubules.

**Diagnosis** The condition was diagnosed as (1) renal calculus and (2) chronic pyelonephritis with hydronephrosis.

**Postoperative Course**—Postoperatively the blood pressure fell from 160 systolic and 100 diastolic to 130 systolic and 85 diastolic in a period of four days. Thereafter the blood pressure ranged between 155 systolic and 90 diastolic and 200 systolic and 120 diastolic, the average level for the four days before the patient's discharge being 175 systolic and 115 diastolic (fig 2).

The patient was readmitted to the hospital on Dec 7, 1942 approximately three months after her discharge

In the interval she had been feeling well. Physical examination gave essentially the same results as on the previous admission. The blood pressure was 230 systolic and 125 diastolic, with rest in bed it promptly fell and stabilized itself at a level of 190 systolic and 100 diastolic (fig 3). Intravenous pyelograms revealed slight enlargement of the remaining right kidney with moderate dilatation of the renal pelvis. It excreted 37 per cent of intravenously injected phenolsulfonphthalein in two hours and concentrated urine to a specific gravity of 1.020. Renal blood flow as measured by the diodist clearance test was 956 cc per minute.

**Comment**—This case points out one of the chief dangers of nephrectomy in the treatment of hypertension. The degree of pyelonephritis was minimal, and there was little functional impairment of the kidney. Therefore, by its removal a considerable increase in functional load was placed on the remaining kidney. The blood pressure promptly rose to levels well above the preoperative range and has remained so to the time of writing. Had it been possible, the procedure of choice in this case would have been removal of the stone and subsequent eradication of the infection in the pelvis of the kidney. Such a course would have avoided the removal of functional renal tissue and for this reason would have been more likely to effect a change in the blood pressure to or toward normal levels.

**CASE 2**—M. A. C., a 37 year old married woman, entered the hospital complaining of headache and high blood pressure. She was first noted to have an increase in blood pressure at the age of 27, in a routine examination for life insurance. Her first three pregnancies resulted in miscarriages, and the fourth pregnancy, two years before her admission to the hospital was associated with an elevation of systolic blood pressure up to 230. There was no history of cardiac insufficiency.

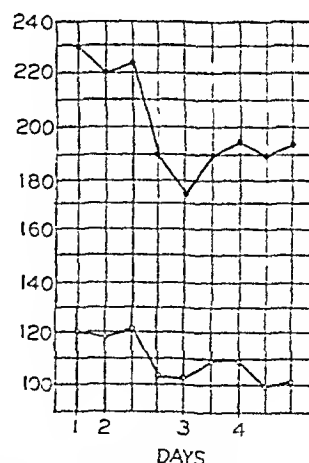


Chart 3 (case 1)—Effect of rest in bed on blood pressure three months after nephrectomy

and no urinary symptoms. For three or four months she had complained of headache with attacks of dizziness and her blood pressure had been persistently elevated.

The physical examination revealed slight blurring of the optic disks with spots of hemorrhage and exudate and marked arteriovenous nicking. There were moderate tachycardia and an inconstant gallop rhythm.

otherwise the results of physical examination were not remarkable

The urine contained albumin (4 plus) and occasional white and red blood cells. Culture of the urine showed no growth. The nonprotein nitrogen content of the blood was 31 mg per hundred cubic centimeters. Forty per cent of intravenously injected phenolsulfonphthalein was excreted in two hours. The urine was concentrated to a specific gravity of 1.015. Intravenous pyelograms showed good function of a normally appearing left kidney. The right renal pelvis was never satisfactorily visualized, and a faint shadow was seen in the region of the upper pole of the right kidney, which was thought to be due to a stone. Retrograde pyelograms of the right kidney showed no definite abnormality, but only 8 per cent of phenolsulfonphthalein was excreted in fifteen minutes.

The blood pressure while the patient was in the hospital at rest in bed averaged 235 systolic and 135 diastolic. On Nov 20, 1942 a nephrectomy was done on the right side by Dr. Fred Garvey. There was an immediate postoperative fall in blood pressure to 190 systolic and 110 diastolic, but this promptly rose to a level of about 220 systolic and 130 diastolic, where it remained until the patient's discharge from the hospital.

*Gross and Microscopic Observations on the Kidney*—*Gross Description* The specimen consisted of the right kidney, which weighed 140 Gm and measured 11 by 6 by 5 cm. The capsule stripped without difficulty. Beneath the capsule were bluish, discolored areas. The cut surface was pale brown. There was no evidence of distortion of the cortical architecture, nor was there evidence of infarction, scars, cysts, cavities or new growths. The cortex measured 5 cm and the medulla 18 cm in thickness. The calices did not present abnormalities, and the papillae were sharp tipped. The renal pelvis contained some fat, but there was no evidence of dilatation of the structure. No stones were present. Approximately 4 cm of the superior portion of the attached ureter was included, and there was no evidence of constriction or dilatation.

*Microscopic Description* Many arterioles of the kidney showed sclerosis with subendothelial deposits of hyalin and thickening of the intima with narrowing of the lumen. An occasional afferent arteriole was observed in which there was an area of early necrosis but necrotic foci were not seen in the glomeruli. A majority of the glomeruli appeared normal, but scattered throughout the cortex were occasional fibrosed glomeruli. A few glomeruli were seen in which the capsular epithelium appeared thickened but no definite epithelial crescents were present. In some areas the renal tubules had been replaced by fibrous tissue, and an occasional dilated tubule was seen. A few tubules were lined by cells which contained pyknotic nuclei. The lesions present in this kidney had a patchy distribution.

*Diagnosis* The diagnosis was arteriolonephrosclerosis with arteriolonecrosis.

Two months after nephrectomy the patient stated that she had noted considerable symptomatic improvement. The headache was much improved. However, the blood pressure, measured at frequent intervals by her physician, remained at the usual preoperative level.

*Comment*—In this case nephrectomy was done because of suggestive pyelographic evidence of unilateral renal disease, and on the chance, admittedly slight, that if this was true some improvement might be gained by the removal of

the kidney. The lesion proved to be arteriolonephrosclerosis, undoubtedly bilateral, and the nephrectomy did not alter the blood pressure.

*CASE 3*—M. C., a 36 year old woman, several years before admission to the hospital had had an attack of pain in both flanks, most severe on the right, and had passed blood in the urine. At that time a cystoscopic examination was made, but no stones were found. She had known for several years that she had a tendency toward an increase in blood pressure. The highest pressure ever found was 178 systolic, but at times it has been as low as 120 systolic. She had had pain under the left costal margin which radiated into the left shoulder and which was not related to exertion.

The significant findings on physical examination were definite tenderness at the right costovertebral angle and a palpable but not necessarily enlarged right kidney.

While the patient was in the hospital the blood pressure varied between 145 systolic and 100 diastolic and 110 systolic and 80 diastolic, the average pressure being about 125 systolic and 90 diastolic. The examination of the urine gave negative results, and the urine was sterile on culture. The maximum specific gravity attained (Fishberg technic) was 1.029. Cystoscopic examination revealed a stone in the right ureter, with marked hydronephrosis and complete destruction of the right kidney.

In February 1941, the right kidney was removed. The blood pressure readings since that time are: April 1941, 140 systolic and 80 diastolic, July 1941, 150 and 80, August 1941, 160 and 100, April 1942, 160 and 80, January 1943, 150 and 105. At the time of the last reading the patient was seven months pregnant and apparently doing well.

*Comment*—In this case the hypertension was minimal, of only a few years' duration and associated with a ureteral stone, severe hydronephrosis and destruction of the kidney. Under these, ordinarily favorable, circumstances removal of the destroyed kidney did not produce any improvement in the hypertension. Two years later the blood pressure was slightly higher than it was before nephrectomy.

*CASE 4*—A 20 year old student first experienced a sudden severe pain in the left upper quadrant of the abdomen in November 1918. The pain gradually decreased in severity over a period of three days, but a sense of soreness in the left upper quadrant, especially when the youth was lying on the left side, persisted for several months. A similar attack occurred in June 1922, and in April 1930, at which time his blood pressure was found to be 190 systolic and 110 diastolic. At this time the physical examination otherwise gave normal results, as did the examinations of the blood and the urine. At about this time he began having persistent pain in the left upper quadrant of the abdomen, an almost constant dull occipital headache and frequent attacks of vertigo. In January 1931, the blood pressure was 210 systolic and 120 diastolic, and from then until November 1935 it ranged between 170 systolic and 110 diastolic and 210 systolic and 120 diastolic. In January 1936, after an acute attack of pain in the left upper abdominal quadrant, he was examined with the cystoscope and the left kidney was found to be enlarged and functionless. The urine was normal, as it had been on frequent examinations since the onset of his illness in

1918 In January 1939, the patient began having angina pectoris, which rapidly became more severe so that he had attacks at rest and required as many as 15 glyceryl trimtrate tablets in a twenty-four hour period for relief. At this time the left kidney began to enlarge rapidly and became palpable almost to the iliac crest. In June 1939 the left kidney was removed. The organ was a large hydronephrotic sac which contained practically no kidney tissue. One branch of the renal artery was found to be constricting the left ureter.

On July 9, 1939 the blood pressure was 110 systolic and 70 diastolic, in January 1940, 125 systolic and 90 diastolic, in February 1943, 138 systolic and 92 diastolic. Since the nephrectomy his blood pressure has been taken every three to four months and has remained at these levels. He has lived an active life and has enjoyed excellent health, without headache, vertigo or angina pectoris.

*Comment*—This case illustrates a favorable result. Although of long duration, the blood pressure was reduced to normal or approximately normal levels (the diastolic pressure remains at or slightly above the upper limits of normal) by the removal of a functionless, hydronephrotic kidney and has remained so for three and one-half years.

TABLE 1—Effect of Nephrectomy on Blood Pressure in Cases Collected from the Literature

Author	Improved			
	Blood Pressure Unimproved	Blood Pressure Reduced but Not to Normal Level	Blood Pressure Reduced to Normal but Followed Less than 2 Years	Blood Pressure Normal After 2 Years or More
Koons and Ruck <sup>70</sup>			1	
Nesbit and Rittell <sup>74</sup>	1	1	6	
Crabtree and Ohaset <sup>71</sup>	10*	2		
Farrell and Young <sup>75</sup>			1	
deTakats and others <sup>71</sup>			2 †	
Powers and Murray <sup>74</sup>		1		
Friedman and others <sup>71</sup>	2	3		
Barney and Suby <sup>74</sup>			1 ‡	
Barker and Walters <sup>70 c</sup>		2	3	
Burkland <sup>74</sup>				1
McIntyre <sup>74</sup>			1	
Boyd and Lewis <sup>71</sup>			1	
Bothe <sup>70</sup>		1		1 ‖
Butler <sup>4</sup>			1 §	
Gibson <sup>74</sup>		1		
Richardson <sup>71</sup>		1	1	
Kennedy and others <sup>74</sup>			1	
Wilson and Chamberlain <sup>74</sup>		1		
Palmer and others <sup>71</sup>	8	1		
Abeshouse <sup>74</sup>	4	9		3
Total	28	23	19	5

\* No follow up on 2 cases not here included  
† No data given  
‡ Followed 21 months  
‖ Inadequate preoperative blood pressure recordings  
§ Followed 20 months

GENERAL COMMENT

Butler,<sup>4</sup> in 1937, reported the case of a 7 year old boy with unilateral pyelonephritis and hypertension, whose blood pressure returned to normal after nephrectomy and had remained so for twenty months. Since then numerous reports of unilateral nephrectomy in the treatment of hypertension have appeared.<sup>2</sup> Seventy-five such cases

from the literature are reviewed in the present report (table 1).

By far the most frequent pathologic condition found in the removed kidneys was chronic pyelonephritis. This condition was present in 48 of the 75 cases (64 per cent). Other pathologic conditions found were renal neoplasms, tuberculosis, calculi and associated pyelonephritis.

TABLE 2—Pathologic Conditions Found in the Removed Kidneys in the Cases Collected from the Literature

Type of Renal Disease	Blood Pressure Improved			Blood Pressure Normal After 2 Years or More	Totals
	Blood Pressure Unchanged	Reduced but Not to Normal	Reduced to Normal but Followed Less than 2 Years		
Chronic pyelonephritis	21	13	13	1	48
Renal tuberculosis	1	3		2	6
Renal calculi and pyelonephritis	1	4	1		6
Aberrant renal artery with hydronephrosis				1*	1
Renal infarction			1		1
Occlusion of renal artery				1	1
Traumatic renal injuries		1	1		2
Hypoplastic kidneys			1		1
Hypernephroma	5	2	1		8
Wilms tumor			1		1
Total	28	23	19	5	75

\* Inadequate preoperative blood pressure readings

with or without hydronephrosis, aberrant renal vessels with hydronephrosis, renal infarction, partial occlusion of the renal artery by a congenital mass of muscle, hypoplastic kidney and lesions of the kidney due to trauma (table 2).

From a review of the isolated case reports one might gain the impression that hypertension in unilateral renal disease is not an uncommon occurrence. However, studies of large series of cases tend to invalidate this impression. Braasch, Walters and Hammer<sup>72</sup> observed hypertension in 18.4 per cent of 1,684 patients who were subjected to renal surgical procedures of all types. Abeshouse<sup>73</sup> found hypertension to be present in 17.3 per cent of 167 patients with unilateral renal disease who were subjected to nephrectomy. Braasch stated that the incidence of unilateral renal disease in patients at the Mayo Clinic who were amenable to treatment was less than 1 per cent, but that the hypertension in such patients had frequently been relieved by operation. The most amenable lesion, he declared, is atrophic pyelonephritis.

From table 1 it can be readily seen that if a two year follow-up period is considered a necessary criterion the incidence of permanent cure in the cases in the literature in which nephrectomy has been done for hypertension is low. Only 5 of the 75 cases (6.6 per cent) fall into



this group (table 3) It is significant that in all of these the patients had minimal hypertension to begin with and were young The duration of the hypertension before operation was two years or less in 3 cases, unknown in 1 case and eight and one-half years in the case of the child reported on by Burkland,<sup>7h</sup> in whom a congenital mass of smooth muscle partially occluded one renal artery In the case of Bothe<sup>7e</sup>

7 (a) Abeshouse, B S Hypertension and Unilateral Renal Disease, *Surgery* **9** 942, 1941, **10** 147, 1941 (b) Barker, N W, and Walters, W Hypertension and Chronic Atrophic Pyelonephritis, *J A M A* **115** 912 (Sept 14) 1940, (c) Hypertension Associated with Unilateral, Chronic Atrophic Pyelonephritis, *Proc Staff Meet, Mayo Clin* **13** 118, 1938 (d) Barney, J D, and Suby, H L Unilateral Renal Disease with Arterial Hypertension Report of a Case, *New England J Med* **220** 744, 1939 (e) Bothe, A E Pyelonephritis in Children and Adults with Hypertension, *J Urol* **42** 969, 1939 (f) Boyd, C H, and Lewis, L G Nephrectomy for Arterial Hypertension, *ibid* **39** 627, 1938 (g) Braasch, W F, Walters, W, and Hammer, H J Hypertension and the Surgical Kidney, *J A M A* **115** 1837 (Nov 30) 1940 (h) Burkland, C E Apparent Cure of Hypertension by Nephrectomy, *J Urol* **46** 638, 1941 (i) Crabtree, E C, and Chaset, N Vascular Nephritis and Hypertension, *J A M A* **115** 1842 (Nov 30) 1940 (j) de Takats, G, Heyer, H E, and Keeton, R W The Surgical Approach to Hypertension, *ibid* **118** 501 (Feb 14) 1942 (k) Farrell, J D, and Young, R H Hypertension Caused by Unilateral Renal Compression, *ibid* **118** 711 (Feb 28) 1942 (l) Friedman, M, Selzer, A, Kreutzmann, H, and Sampson, J J The Changes in the Blood Pressure and in the Renal Blood Flow and Glomerular Filtration Rate of Hypertensive Patients Following Unilateral Nephrectomy, *J Clin Investigation* **21** 19, 1942 (m) Gibson, T E Hypertension and the Surgical Kidney, *California & West Med* **56** 66, 1942 (n) Kennedy, R L J, Barker, N W, and Walters, W Malignant Hypertension in a Child Cure Following Nephrectomy, *Am J Dis Child* **61** 128 (Jan) 1941 (o) Koons, K M, and Ruck, M K Hypertension in a Seven-Year Old Girl with Wilms' Tumor Relieved by Nephrectomy, *J A M A* **115** 1097 (Sept 28) 1940 (p) Leadbetter, W F, and Burkland, C E Hypertension in Unilateral Renal Diseases, *J Urol* **39** 611, 1938 (q) McIntyre, D W Unilateral Chronic Pyelonephritis with Arterial Hypertension, *ibid* **41** 900, 1939 (r) Nesbit, R M, and Ratliff, R K Hypertension Associated with Unilateral Nephropathy, *ibid* **43** 427, 1940 (s) Nesbit, R M, and Ratliff, R K Hypertension Associated with Unilateral Renal Disease, *J A M A* **116** 194 (Jan 18) 1941 (t) Palmer, R S, Chute, R, Crone, N L, and Castleman, B The Renal Factor in Continued Arterial Hypertension Not Due to Glomerulonephritis, as Revealed by Intravenous Pyelography, *New England J Med* **223** 165, 1940 (u) Powers, J H, and Murray, M F Juvenile Hypertension Associated with Unilateral Lesions of the Upper Urinary Tract, *J A M A* **118** 600 (Feb 21) 1942 (v) Richardson, G O, and Smart, G A Nephrectomy in Unilateral Renal Disease with Hypertension, *Lancet* **2** 594, 1941 (w) Wilson, C L, and Chamberlain, C T Unilateral Renal Ischemia Associated with Hypertension Case Report, *J Urol* **47** 421, 1942

preoperative recordings of the blood pressure were made only twice and can hardly be considered adequate In this case it is questionable whether hypertension ever actually existed

Nineteen (25.3 per cent) of the 75 patients presented a reduction in blood pressure to normal levels after nephrectomy but when reported on they had been followed for only a few weeks to twenty-one months after operation and hence cannot be considered permanently cured It is safe to predict that a number of patients in this group will subsequently show a return of the blood pressure to hypertensive levels Twenty-three (30.6 per cent) of the 75 patients showed a reduction in blood pressure after nephrectomy but the pressure failed to return to normal levels In their cases it is difficult to be certain of the effect of the nephrectomy itself on the subsequent course of the hypertension The depressor effect of rest in bed alone, and particularly of rest in bed plus any surgical procedure, has previously been referred to One must therefore be cautious in crediting a partial or temporary reduction in blood pressure to a specific operative procedure (such as nephrectomy)

Finally, in 28 (37.3 per cent) of the 75 patients no reduction in blood pressure was observed after nephrectomy

Thus, 31.9 per cent, or approximately one third, of the patients whose cases form the basis for this report can be considered to have shown a reduction in blood pressure to normal levels following unilateral nephrectomy However, only 5 of these patients have been followed for as long as two years after operation and can be considered permanently cured Final evaluation of the results for the remaining patients must be deferred until sufficient time has elapsed to determine with more certainty whether the blood pressure has been permanently reduced to normal levels One third of the patients have shown a reduction in blood pressure, but never to normal levels, and still remain hypertensive The patients in this group, however, usually experienced considerable symptomatic improvement

Recent experimental observations are of interest in this regard Friedman, Jarman and Klemperer<sup>8</sup> produced sustained hypertension in rats by means of unilateral renal injury Subsequent removal of the injured kidney from the hypertensive animals resulted in a decline in blood pressure but not to the previous normal levels This elevation of blood pressure was

8 Friedman, B, Jarman, J, and Klemperer, P Sustained Hypertension Following Experimental Unilateral Renal Injuries Effects of Nephrectomy, *Am J M Sc* **202** 20, 1941

maintained for long periods after the injured kidney had been removed. Grollman, Harrison and Williams<sup>9</sup> observed that application of cloth or collodion to one kidney caused hypertension in a small percentage of otherwise normal rats and that subsequent removal of the kidney did not result in a significant decline in blood pressure. Furthermore, they observed that removal of one kidney from normal rats occasionally resulted in a slight but measurable rise in blood pressure.

Finally, in one third of the cases no change was observed after nephrectomy, or the hypertension was made definitely worse by the operation. Three of the additional cases reported here fall into this group and are included to point out the dangers of nephrectomy for persons with hypertensive disease and to emphasize the necessity for careful study of all patients suspected of having unilateral renal disease and hypertension before nephrectomy is done. As has been indicated,

removal can be expected to alter the blood pressure appreciably. The opposite kidney, on the other hand, must be functioning normally so far as its function can be measured by means of pyelography and by the recognized clinical measures of renal function. Careful bacteriologic study of the urine from the normal kidney must be made before one can be certain of the absence of infection.

In regard to the evaluation of renal function, a recent report by Chasis and Redish<sup>10</sup> aptly pointed out that most of the common tests of renal function, including pyelography, may at times be unreliable. By correlating the results of pyelography and of other tests of renal function of the separate kidneys of 21 hypertensive patients, they were able to demonstrate that inequality in flow of urine can readily lead to misinterpretation of the results of excretory tests of renal function. The results of dye concentration tests may differ for the two kidneys, yet

TABLE 3—Five Cases from the Literature in Which the Blood Pressure Had Remained Normal For at Least Two Years After Nephrectomy

Author	Age	Pre-operative Blood Pressure	Post-operative Blood Pressure	Duration of Hypertension	Years After Operation	Pathologic Diagnosis
Burkland <sup>7b</sup>	9	155/105	105/65	8.5 years	3.5	Hypoplastic ectopic pelvic kidney with partial occlusion of renal artery by congenital mass of smooth muscle
Bothe <sup>7a</sup>	7	130/90-130/85	110/65	Unknown	4.5	Aberrant renal vessels with hydro-nephrosis
Abeshouse <sup>7a</sup>	21	148/86	120/80	1 year	4	Tuberculosis
	29	144/92-150/96	122/78	1 year	2	Tuberculosis
	35	140/84-160/100	135/80	2 years (?)	7.5	Chronic pyelonephritis hydro-nephrosis

the incidence of hypertension in unilateral renal disease in patients who are amenable for treatment (nephrectomy) is low, and more careful selection of patients for the operation is necessary if a reasonable success is to be attained.

In any case in which unilateral renal disease is suspected and in which nephrectomy is contemplated it is obvious that the functional status of both kidneys is of utmost importance and must be carefully appraised. This is especially true if hypertension exists, for the removal of one kidney, if it retains any function at all, will place an increased load on the remaining organ, which, if its function is but slightly impaired, will result in relative or functional ischemia of that organ. In such a case there can be little hope of effecting any permanent change in the blood pressure. It follows, then, that the diseased kidney should be functionless or practically so before its re-

moval can be expected to alter the blood pressure appreciably. The opposite kidney, on the other hand, must be functioning normally so far as its function can be measured by means of pyelography and by the recognized clinical measures of renal function. Careful bacteriologic study of the urine from the normal kidney must be made before one can be certain of the absence of infection.

Furthermore, the age of the patient and duration of the hypertension should be given careful consideration, for the older the patient and the longer the duration of the hypertension the greater is the likelihood that arteriosclerotic and arteriolosclerotic changes have occurred in the opposite kidney. As has been emphasized when

<sup>9</sup> Grollman, A., Harrison, T. R., and Williams, J. R. The Mechanism of Experimental Renal Hypertension in the Rat. The Relative Significance of Pressor and Anti-Pressor Factors, to be published.

<sup>10</sup> Chasis, H., and Redish, J. Function of the Separate Kidneys in Hypertensive Subjects, *Arch. Int. Med.* 70:728 (Nov.) 1942.



there is disease present in the remaining kidney which impairs its function there can be little hope that nephrectomy will effect any lasting improvement in the hypertension. Of equal importance is the functional status of the kidney to be removed. Unless this organ is functionless or its function is markedly diminished, its removal can be expected to result in an increase in the severity of the hypertension rather than in a reduction of the blood pressure toward normal.

The following criteria for the selection of patients with hypertension for whom nephrectomy is indicated should be rigidly met if reasonable success is to be obtained:

- 1 The diseased kidney should be functionless or its function greatly diminished.
- 2 The opposite kidney should function normally.
- 3 The hypertension should be of short duration.
- 4 Other factors being equal, the younger the patient, the greater the chances of favorable results following nephrectomy.

It should be pointed out that even though these criteria are met there can be no certainty that a favorable response will be obtained. This fact is illustrated in case 2 reported here. However, if in the future cases are selected with care and with proper evaluation of the factors that have been discussed, the percentage of favorable results should be increased, and those instances in which the hypertension is made worse by nephrectomy may be avoided.

#### SUMMARY

Only 5 of the 75 cases of hypertension taken from the literature meet the requirements for cure after nephrectomy. Approximately one third of the patients had a fall in blood pressure to normal levels but had been followed for less than two years at the time their cases were reported. One third had a reduction in blood pressure but remained hypertensive, while in one third the blood pressure was unchanged or increased in severity.

The most common pathologic condition in the removed kidneys was chronic pyelonephritis.

A two year follow-up period is necessary before hypertension can be considered cured by nephrectomy.

Cases in which unilateral nephrectomy is indicated for hypertension are rare, and there is need for more careful selection of such cases.

The removal of a kidney, if it retains any function at all, is likely to increase the severity of the hypertension rather than to improve it. This is true even though the function of the opposite kidney is entirely normal.

The usual tests of renal function may at times be unreliable,<sup>3</sup> and in the light of this fact special care and consideration must be given to evaluation of the function of each kidney before nephrectomy is performed.

The age of the patient and the duration of the hypertension are additional factors of importance in the selection of suitable cases for nephrectomy in the treatment of hypertension.

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# A NEW AID IN CONTROL OF HEMORRHAGE IN SEVERE DAMAGE TO THE LIVER

TRANSFUSIONS OF BLOOD FORTIFIED BY ADMINISTRATION OF VITAMIN K TO DONORS

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The study of vitamin K and its relation to coagulation of blood has been completed in many of its details, with most of the research following three lines of investigation

The first is based on the work of Dam,<sup>1</sup> who observed that when chicks were placed on a diet low in fat, a hemorrhagic disease developed. He demonstrated that this was a specific avitaminosis and that the bleeding tendency was due to hypoprothrombinemia. It has been further shown that this deficiency can be cured by feeding extracts of alfalfa or putrefied fish meal.

The second is based on the well known fact that patients with obstructive jaundice and biliary fistula acquire hemorrhagic tendencies and that the likelihood of bleeding increases with the length of time and the completeness with which bile is excluded from the intestinal tract. Warner, Brinkhous and Smith<sup>2</sup> and Butt, Snell and Osterberg<sup>3</sup> almost simultaneously reported the efficacious therapeutic use of vitamin K in treatment of bleeding due to jaundice. Since then there have been many reports<sup>4</sup> of the

therapeutic value of vitamin K against hypoprothrombinemia due to obstructive jaundice, biliary fistula and mild to moderate damage of the liver.

The third is based on the observations of Brinkhous, Smith and Warner,<sup>5</sup> who reported that there is a uniform reduction in the plasma prothrombin levels in the newborn throughout infancy. This hypoprothrombinemia sometimes reaches the hemorrhagic level in a newborn infant even though the mother's concentration of prothrombin has remained normal during the pregnancy and delivery.<sup>6</sup> Many authors have reported that the hypoprothrombinemia of the newborn responds readily to vitamin K<sup>7</sup> and that the deficiency of prothrombin in the new-

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1 Dam, H. Hemorrhages in Chicks Reared on Artificial Diets. New Deficiency Disease, Nature, London **133**:909 (June 16) 1934.

2 Warner, E. D., Brinkhous, K. M., and Smith, H. P. Bleeding Tendency of Obstructive Jaundice. Prothrombin Deficiency and Dietary Factors, Proc Soc Exper Biol & Med **37**:628 (Jan) 1938.

3 Butt, H. R., Snell, A. M., and Osterberg, A. E. The Use of Vitamin K and Bile in Treatment of the Hemorrhagic Diathesis in Cases of Jaundice, Proc Staff Meet, Mayo Clin **13**:74 (Feb 2) 1938.

4 (a) Stewart, J. D., and Rourke, G. M. Control of Prothrombin Deficiency in Obstructive Jaundice by Use of Vitamin K, J A M A **113**:2223 (Dec 16) 1939. (b) Stewart, J. D. Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, Ann Surg **109**:588 (April) 1939. (c) Allen, J. G., and Julian, O. C. Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, *ibid* **41**:1363 (Dec) 1940. (d) Greene, C. H. Liver and Biliary Tract. A Review of 1940, Arch Int

Med **67**:867 (April) 1941. (e) Butt, H. R., Snell, A. M., and Osterberg, A. E. The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, J A M A **113**:383 (July 29) 1939. (f) Pohle, F. J., and Stewart, J. K. Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, J Clin Investigation **19**:365 (March) 1940. (g) Lord, J. W., Jr., Andrus, W. DeW., and Moore, P. A. Metabolism by Vitamin K and Role of the Liver in Production of Prothrombin in Animals, Arch Surg **41**:585 (Sept) 1940. (h) Warner, E. D. Prothrombin Effect of Partial Hepatectomy, J Exper Med **68**:831 (Dec) 1938.

5 Brinkhous, K. M., Smith, H. P., and Warner, E. D. Plasma Prothrombin Level in Normal Infancy and in Hemorrhagic Disease of the Newborn, Am J M Sc **193**:475 (April) 1937.

6 (a) Stewart, J. D. Clinical Significance of Prothrombin Deficiency and Its Treatment, Ann Surg **114**:907 (Nov) 1931. (b) Shettles, L. B., Delfs, E., and Hellman, L. M. Factors Influencing Plasma Prothrombin in the Newborn Infant. II. Antepartum and Neonatal Ingestion of Vitamin K Concentrate, Bull Johns Hopkins Hosp **65**:419 (Nov) 1939.

7 (a) Brinkhous, K. M. Plasma Prothrombin. Vitamin K, Medicine **19**:329 (Sept.) 1940. (b) Beck, A. C., Taylor, E. S., and Colburn, R. F. Vitamin K Administered to the Mother During Labor as a Prophylaxis Against Hemorrhage in the Newborn Infant, Am J Obst & Gynec **41**:765 (May) 1941. (c) McCready, R. L., Callahan, E. T., and Grandin, D. J. Parenteral Vitamin K Therapy in Antepartum Women and Its Effects on the Infants' Prothrombin Levels, *ibid* **42**:398 (Sept.) 1941. (d) Pray, L. G., McKevon, H. S., and Pollard, W. E. Hemorrhagic Diathesis of the Newborn, *ibid* **42**:836 (Nov) 1941. (e) Stewart, J. D. (f) Shettles, Delfs and Hellman.<sup>6b</sup>

born infant can be prevented by administering vitamin K to the mother a few hours before delivery<sup>6</sup> When the amount of prothrombin was normal in the mother, there was little or no change after administering vitamin K

One of the problems now remaining in this field is the control of hemorrhage associated with severe damage to the liver<sup>8</sup> Bollman, Butt and Snell<sup>8b</sup> stated that "severe hepatic injury is invariably associated with a deficiency of prothrombin in the circulating blood If the hepatic injury is severe enough, the administration of vitamin K is not effective in correcting this deficiency of prothrombin" Kark and Souter<sup>9</sup> concluded that the lowered prothrombin level in severe widespread hepatic damage will remain below hemorrhagic level despite vitamin K therapy and that when the prothrombin remains below 30 to 35 per cent of normal after vitamin K therapy the outlook is grave Ziffren, Owen, Warner and Peterson,<sup>8c</sup> after wide clinical use of vitamin K, expressed the opinion that disease of the liver interferes with response of the prothrombin level to vitamin K therapy in human patients Allen and Julian<sup>4c</sup> cited 10 cases of intrahepatic jaundice without response to vitamin K and 2 with delayed response Abbott and Holden<sup>8e</sup> studied 12 cases of moderately far advanced Laennec cirrhosis of the liver with prothrombin values ranging from 40 to 86 per cent of normal Several patients received vitamin K, without response In 1 case the prothrombin level gradually lowered from 40 to 25 per cent of normal in spite of vitamin K and the patient finally died from hepatic failure Stewart and Rourke<sup>4a</sup> stated "In general terms, the longer the duration of the jaundice and the greater the liver damage, the lower the plasma prothrombin concentration" Stewart<sup>4b</sup> expressed the opinion that the hypoprothrombinemia in hepatic disease

is not proportionate to the jaundice and that in the acute, severe diseases, such as acute yellow atrophy, the prothrombin deficiency frequently reaches the hemorrhagic zone The experimental evidence in support of the role played by the liver in the production of prothrombin is to be found in the work of Andrus and his colleagues<sup>10</sup> and of Warren and Rhoads,<sup>11</sup> who by total and partial hepatectomy in animals produced profound hypoprothrombinemia which was not affected by vitamin K or bile salts

Allen and Vermeulen<sup>12</sup> stated "It would appear that prothrombin is actively destroyed in vivo, at least when the liver is damaged or removed" They cited the case of a patient with an external biliary fistula who had spontaneous hemorrhages fourteen months after development of the fistula and was given 7,200 cc of blood in thirty-six hours, with control of the bleeding However, in two days spontaneous bleeding recurred, despite the fact that the amount of blood given by transfusion approximated the calculated total blood volume They emphasized the futility of transfusion alone in combating hemorrhage due to hypoprothrombinemia If vitamin K fails to increase the prothrombin, Kark and Souter<sup>9</sup> pointed out, there are only two other therapeutic measures available—transfusions of fresh blood or of fresh plasma According to Stewart,<sup>4a</sup> a 500 cc transfusion of average whole blood to a patient with moderate hypoprothrombinemia may be expected to effect a transitory rise in the adult patient's plasma concentration of about 10 per cent Andrus and Lord<sup>13</sup> cited a case of thrombosis of the hepatic artery and the portal vein with massive necrosis of the liver in which the prothrombin content remained around 25 per cent of normal in spite of administration of vitamin K and transfusions Apparently in this case transfusions of whole blood had little effect on the prothrombin Lord and Andrus<sup>14</sup> reported that the plasma prothrombin falls to

8 (a) Smith, H P, Warner, E D, and Brinkhous, K M Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J Exper Med* **66** 801 (Dec) 1937 (b) Bollman, J L, Butt, H R, and Snell, A M The Influence of the Liver on the Utilization of Vitamin K, *J A M A* **115** 1087 (Sept 28) 1940 (c) Ziffren, S E, Owen, C A, Warner, E D, and Peterson, F R Hypoprothrombinemia and Liver Function, *Surg, Gynec & Obst* **74** 463 (Feb, no 2A) 1942 (d) Sweet, N J, Lucia, S P, and Aggeler, P M The Clinico-Pathologic Correlation Between Hepatic Damage and the Plasma Prothrombin Concentration, *Am J M Sc* **203** 665 (May) 1942 (e) Abbott, W E, and Holden, W D Prothrombin Test as a Diagnostic and Prognostic Aid, *Arch Surg* **45** 261 (Aug) 1942 (f) Stewart<sup>4a</sup> (g) Allen and Julian<sup>4c</sup> (h) Greene<sup>4d</sup> (i) Butt, Snell and Osterberg<sup>4e</sup> (j) Pohle and Stewart<sup>4f</sup> (k) Shettles, Delfs and Hellman<sup>6b</sup> (l) Brinkhous<sup>7a</sup>

9 Kark, R, and Souter, A W Response to Vitamin K—A Liver Function Test, *Lancet* **2** 693 (Dec 6) 1941

10 Andrus, W DeW, Lord, J W, and Moore, R A The Effect of Hepatectomy on Plasma Prothrombin and the Utilization of Vitamin K, *Surgery* **6** 899 (Dec) 1939

11 Warren, R, and Rhoads, J E Hepatic Origin of the Plasma Prothrombin, *Am J M Sc* **198** 193 (Aug) 1939

12 Allen, J G, and Vermeulen, C Destruction of Prothrombin and Storage of Vitamin K, *Arch Surg* **42** 969 (June) 1941

13 Andrus, W DeW, and Lord, J W Clinical Investigations of Some Factors Causing Prothrombin Deficiencies Significance of the Liver in Their Production and Correction, *Arch Surg* **41** 596 (Sept) 1940

14 Lord, J W, and Andrus, W DeW Differentiation of Intra and Extra Hepatic Jaundice Response of the Plasma Prothrombin to Intramuscular Injection of Menadione (2-Methyl-1,4-Naphthoquinone) as a Diagnostic Aid, *Arch Int Med* **68** 199 (Aug) 1941

10 per cent of normal fourteen hours after hepatectomy in animals. They were of the opinion that jaundice was of intrahepatic type if after 2 mg of menadione was given there was less than 10 per cent rise in prothrombin in twenty-four hours and less than 15 per cent in forty-eight hours.

During the past year 663 cases of intrahepatic jaundice<sup>15</sup> have been observed at the Station Hospital at Camp Blanding. Five of the patients had acute yellow atrophy, with the plasma prothrombin reduced to such an extent that severe spontaneous hemorrhages occurred. These patients were given large doses of vitamin K, without response, and large transfusions of whole blood, with minimal changes in the prothrombin and no effect on the bleeding. The first of these 5 patients was given 10 to 30 mg of menadione intramuscularly and 1,000 to 2,000 cc of whole blood daily. In spite of this, the prothrombin fell to 8 per cent of normal, the bleeding increased and the patient died from generalized hemorrhages and hepatic failure. Autopsy revealed a small liver with severe yellow atrophy and large generalized hemorrhages. In view of this case and of reports by other investigators of the failure of severely damaged livers to respond to vitamin K, it was decided to try transfusions of blood fortified by administration of vitamin K to the donors. This method was suggested by the obstetrician's administration of vitamin K to the mother prior to delivery, even though her prothrombin level is normal, to prevent deficiency of prothrombin in the newborn infant.

#### METHOD

*Preparation of Donors*—Healthy white men with prothrombin levels between 90 and 100 per cent of normal were selected, and their blood was cross matched with the patients'. Determinations of prothrombin, hemoglobin, white blood cell count, sedimentation rate and serologic reaction for syphilis were made for each donor. In most cases the determination of prothrombin was repeated immediately prior to withdrawal of blood for the transfusion. Donors in cases 1 and 2 were given 18 mg of menadione (2-methyl-1,4-naphthoquinone) intramuscularly within the twenty-four hours prior to the transfusion. During this time the donor was allowed twelve hours rest, fluids were limited to 2,500 cc, ingestion of alcohol was not allowed and an adequate diet was consumed. In the third and fourth cases the procedure varied. Some donors received orally 20 to 30 mg of menadione with bile salts within forty-eight hours of the transfusion. Others received 6 to 12 mg of menadione in aqueous solution intravenously, and still others received 18 mg of menadione in oil intramuscularly. One donor received only 3.2 mg of menadione intramuscularly six hours before the transfusion. Two donors received natural vitamin K derived from fish meal. No ill effects on the donors were

noted in any case. The prothrombin content in the blood of the donors remained essentially the same before and after they received vitamin K.

*Determination of Prothrombin*—Unfortunately, determinations of prothrombin could not be made as frequently as desired, and it was necessary to use two methods. In the tables the values followed by an asterisk were determined by the Quick method<sup>16</sup>. By this method 5 cc of blood was carefully withdrawn in a tube containing 0.5 cc of 1.34 per cent solution of sodium oxalate. The test was made in duplicate with a control. Unfortunately, when this method was used the same control was not always available. The test was performed by mixing in a small test tube 0.1 cc of plasma and 0.1 cc of thromboplastin extract (Difco). To this 0.1 cc of calcium chloride solution (1.11 Gm of anhydrous chemically pure calcium chloride dissolved in 400 cc of distilled water) was added, and the mixture was agitated for five seconds in a water bath. The coagulation time of the normal control in these tests was usually fourteen seconds. The end point was considered to be the point when the mixture failed to run down the side of the tube.

The values determined by the Smith bedside method<sup>17</sup> are not marked in the tables. This technique was as follows. In a 3 cc test tube was placed 0.1 cc of thromboplastin solution (Difco). Freshly drawn blood was then added up to the 1 cc mark. The tube was inverted once and then tilted gently until clotting was complete, as evidenced by failure of the blood to run down the tube in a changed position. A determination on blood of the same normal control (R. K.) was made with each test. The usual prothrombin time of the control was between nineteen and twenty-five seconds. Clotting activity is expressed as a percentage of normal. A value of 80 to 100 per cent is considered normal.

#### REPORT OF CASES

**CASE 1**—B. S., a 24 year old Negro, was admitted to the hospital June 1, 1942, because of anorexia, postprandial epigastric distress, weakness and dark urine of four days' duration. His past health had been good, and there had been no previous episodes of jaundice. He did not use alcohol or tobacco in any form. On examination on admission he appeared well developed and well nourished but somewhat ill. There was moderate jaundice of the scleras and mucous membranes. The heart, lungs, spleen and liver were essentially normal. The stools were light but contained some bile, the urine was dark and contained a large amount of bile. The hemoglobin content and the red blood cell count were normal, the white blood cell count was 4,300, the Kahn reaction was negative, and the icteric index was 57. The course was gradually downhill for the first two weeks, but after that the patient rapidly grew worse. On June 25 the administration of 64 mg of menadione intramuscularly daily was started because the prothrombin content was 42 per cent of normal. By June 29 the hepatic liver dullness had diminished to 2 cm above the costal margin, the icteric index had mounted to 361, and a hemorrhagic tendency had developed. Severe bleeding now occurred after he

16 (a) Quick, A. J. The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin, *Am J Physiol* **118**:269 (Feb) 1937. (b) Quick, A. J. Determination of Prothrombin *Proc Soc Exper Biol & Med* **42**:788 (Dec) 1939.

17 Smith, H. P., Ziffren, S. E., Owen, C. A., and Hoffman, G. R. Clinical and Experimental Studies on Vitamin K. *J A M A* **113**:380 (July 29) 1939.

15 The Outbreak of Jaundice in the Army, Circular Letter No. 95, Office of the Surgeon General, Army Medical Bulletin, 1942, no. 64 p. 179.

cleaned his teeth or ate any food. The following morning the patient was stuporous, and by afternoon he was comatose. The patient was given 1,500 cc of fresh plasma with 50 per cent prothrombin content daily from June 29 to July 2, and on July 2, 3 and 4 he was given 1,000 cc of plasma and 500 cc of whole blood. In spite of this therapy, the bleeding continued to increase, the prothrombin time was 18 per cent of normal, and on July 4 the condition of the patient became critical. It was decided to give a donor large doses of vitamin K and give the patient a transfusion of his blood. On July 5 there was bleeding from the gums, throat, urinary tract and rectum. The following day, July 6, the bleeding had increased. The patient was given a transfusion from the prepared donor, and the bleeding gradually ceased over a period of four hours, with the prothrombin increasing from 8 per cent to 34 per cent of normal. Table 1 lists the transfusions and their effects on the bleeding and on the prothrombin content. The patient received transfusions

was less than one-half the normal size, with almost no hepatic cells remaining, owing to the severe yellow atrophy, there were marked degeneration of the corpus striatum, extensive bronchopneumonia and almost complete disappearance of striated muscle tissue.

CASE 2—B M G, a 29 year old white man, was admitted to the hospital June 24, 1942, with complaint of having noticed anorexia, malaise and "yellow color of the skin" for the past three days. His general health had always been excellent. He was accustomed to drink about two bottles of beer each week and to smoke a package of cigarets daily. There had been no previous attacks of jaundice or other serious illnesses.

The patient was a tall, rather thin blond, who appeared somewhat lethargic. On physical examination there was marked icterus of the scleras, mucous membranes and skin, the edge of the liver extended 2 cm below the costal margin, and at times the patient was euphoric. The hemoglobin content was 90 per

TABLE 1—Effects of Transfusions on Bleeding and on Prothrombin Level in Case 1

Date	Amount of Reenforced Blood, Cc	Amount of Whole Blood, Cc	Prothrombin Before Transfusion, Percentage of Normal	Prothrombin After Transfusion, Percentage of Normal	Time Between Transfusion and Determination of Prothrombin, Hr	Effect on Bleeding in 24 Hours	Bleeding Tendency
7/ 4/42		500	18*			0	Oral, gastrointestinal, renal and subcutaneous hemorrhages
7/ 5/42						0	Oral, gastrointestinal, renal and subcutaneous hemorrhages
7/ 6/42	500		8	34	4	Ceased	Oral, gastrointestinal, renal and subcutaneous hemorrhages
7/ 7/42	500			46	4	0	No bleeding
7/ 8/42	500		49	65	6	0	No bleeding
7/10/42	500		52	68	6	0	No bleeding
7/15/42	500		40*	58*	6	0	No bleeding
7/17/42	500		40*	63*	6	0	No bleeding
8/24/42		500	19	22	6	0	Oral bleeding
8/25/42		500	10	12	4	0	More severe oral and rectal bleeding
8/25/42	500		12	31	4	Ceased	More severe oral and rectal bleeding
8/25/42				52	8	0	No bleeding
8/26/42				55	24	0	Reaction to transfusion no bleeding
8/27/42				44	50	0	No bleeding
8/28/42	500		15	45	12	Ceased	Severe oral and gastrointestinal bleeding
8/29/42	500		42*	63*	8	0	No bleeding
8/30/42	500			75*	24	0	No bleeding
8/31/42	500		75*	75*	4	0	No bleeding

\* Determined by Quick method (other values obtained by the Smith "bedside" technic)

and plasma at other dates, without bleeding, which are not listed in the table because determinations of prothrombin were not made.

During the early part of August, the patient showed many of the usual signs of progressive lenticular degeneration. There were tremors, affective mental disturbances, dysarthria, dysphagia and hypertonia of the extremities, without evidence of involvement of the pyramidal tracts. Fleischner bodies were not observed. The patient had further bleeding on August 24, with a prothrombin content of 35 per cent of normal. Transfusion of 500 cc of whole blood and 1,000 cc of fresh plasma had no effect on the bleeding and a minimal effect on the prothrombin level. The bleeding grew worse, and more fresh blood and plasma had little effect, but in the afternoon of August 25, 500 cc of fortified blood controlled the bleeding in four hours and increased the prothrombin to 52 per cent of normal in eight hours.

There was a moderately severe thermal reaction to fortified transfusion on August 26, and transfusion was omitted on August 27, only to have bleeding develop the following day. This was again controlled by fortified transfusions and kept under control until the patient's death, September 11. At autopsy the liver

cent, the red blood cell count 4,500,000 and the white blood cell count 10,200. The icteric index was 66, the urine contained bile but otherwise was normal, the stools were light in color but contained some bile. The nonprotein nitrogen content of the blood was 35 mg per hundred cubic centimeters, the cholesterol content 160 mg and the total protein 6.4 Gm, the prothrombin content was 75 per cent of normal, and the Kahn reaction was negative.

By July 7, the icteric index had increased to 200, the patient was stuporous and a persistent mild purpuric rash had developed. The prothrombin had decreased to 40 per cent of normal. The patient was given 96 mg of menadione intramuscularly daily, but the prothrombin level continued to fall and the purpuric rash remained unchanged. On July 10, the prothrombin content was 30 per cent of normal, and 500 cc of whole blood and 1,000 cc of fresh plasma were given along with 96 mg of menadione. There was no effect on the prothrombin, and later a few hemorrhages developed in the skin and mucous membranes from minimal trauma. Table 2 enumerates the transfusions and determinations of prothrombin.

On July 11, the patient was almost comatose, and there were oral, urinary and large subcutaneous hem-

orrhages and a prothrombin level of 18 per cent of normal. A transfusion of 500 cc of fortified blood controlled the bleeding within three hours and increased the prothrombin content to 50 per cent of normal in twenty-four hours. The patient received 64 to 96 mg of menadione and 1,000 to 1,500 cc of plasma daily, but on July 21 there was a recurrence of the oral and urinary bleeding. Unfortunately, determinations of prothrombin were not done during this bleeding episode, but suffice it to say that the bleeding was controlled by fortified transfusions. The patient had severe generalized hemorrhages on July 27, with a prothrombin value of 16 per cent of normal, approximately sixty hours after the last fortified transfusion. Again the hemorrhages were controlled by fortified transfusion, but the patient died the following day from an acute overwhelming staphylococcal septicemia. At autopsy, the liver was larger than normal and there were areas of severe yellow atrophy, with large areas of regeneration.

CASE 3—W B R, a 38 year old white man, was admitted to the hospital Sept 8, 1942, for drowsiness,

30 the man began complaining rather suddenly of dyspnea without exertion and of orthopnea, and it was noted that there was minimal generalized edema. Later in the day the patient became cyanotic and then comatose. Although the coma and cyanosis responded to oxygen, the edema had increased and there was rather severe ascites. The total plasma protein content was 6 Gm per hundred cubic centimeters, the albumin-globulin ratio being 25 to 35, the urine showed albumin (1 plus) and numerous casts, the prothrombin content was 46 per cent of normal. The liver had remained essentially the same size, but the spleen was much larger, and there were numerous moist rales over the lower half of each lung. Because of the mild hypoproteinemia with reversal of the albumin-globulin ratio, the generalized edema and the lowered prothrombin level, the patient was given 1,000 cc of plasma and 10 mg of menadione intramuscularly daily from September 30 to October 5, without any apparent effect on the edema, even though there were an increase in the plasma protein and a moderate increase in urinary output. The vitamin K had no

TABLE 2—Effects of Transfusions on Bleeding and on Prothrombin Level in Case 2

Date	Amount of Reenforced Blood, Cc	Amount of Whole Blood, Cc	Prothrombin Before Transfusion, Percentage of Normal	Prothrombin After Transfusion, Percentage of Normal	Time Between Transfusion and Determination of Prothrombin, Hr	Effect on Bleeding in 24 Hours	Bleeding Tendency
7/10/42		500	23*	28*	6		Few hemorrhages in skin from mild trauma
7/11/42	500		13*	36*	4	Ceased	Marked subcutaneous, oral and renal bleeding
7/12/42				50*	24	0	No bleeding
7/13/42	500		34	47	4	0	No bleeding
7/15/42	500		33	50	6	0	No bleeding
7/16/42	500		53	62	4	0	No bleeding
7/21/42	500					Ceased	Oral and renal bleeding
7/22/42	500					0	No bleeding
7/23/42	500		28*	43*	12	0	No bleeding
7/24/42	500			48*	8	0	No bleeding
7/25/42	500		42*	50*	4	0	No bleeding
7/27/42	500		16	38	6	Ceased	Oral, gastrointestinal, renal and subcutaneous (hematomas)

\* Determined by Quiek method (other values obtained by the Smith "bedside" technique)

jaundice, general malaise, anorexia, light stools and dark urine of seven days' duration. The patient had been a heavy imbibor of beer and whisky for over ten years. His brothers stated that he had had four attacks of jaundice lasting about ten days following severe alcoholic debauches. He had been drinking about a pint of whisky and five to ten bottles of beer daily for three months before admission.

The initial physical examination revealed a rather short, stout man who appeared much older than his given age. The liver extended 5 cm below the costal margin and was firm but not tender. The spleen was easily palpable, even though there was pronounced abdominal distention. There was a soft blowing apical systolic cardiac murmur. The skin, mucous membranes and scleras were extremely icteric. The hemoglobin content was 70 per cent, the red blood cell count 3,700,000, the white blood cell count 6,500, the icteric index 100, the Kahn reaction negative and the non-protein nitrogen content 35 mg and the urea content 15 mg per hundred cubic centimeters. The urine contained much bile, a small amount of albumin and a few granular casts, the stools were brown and contained an approximately normal amount of bile.

During the first three weeks of the patient's hospitalization, the icteric index gradually increased to 154, but otherwise there was little change. On September

30 the man began complaining rather suddenly of dyspnea without exertion and of orthopnea, and it was noted that there was minimal generalized edema. Later in the day the patient became cyanotic and then comatose. Although the coma and cyanosis responded to oxygen, the edema had increased and there was rather severe ascites. The total plasma protein content was 6 Gm per hundred cubic centimeters, the albumin-globulin ratio being 25 to 35, the urine showed albumin (1 plus) and numerous casts, the prothrombin content was 46 per cent of normal. The liver had remained essentially the same size, but the spleen was much larger, and there were numerous moist rales over the lower half of each lung. Because of the mild hypoproteinemia with reversal of the albumin-globulin ratio, the generalized edema and the lowered prothrombin level, the patient was given 1,000 cc of plasma and 10 mg of menadione intramuscularly daily from September 30 to October 5, without any apparent effect on the edema, even though there were an increase in the plasma protein and a moderate increase in urinary output. The vitamin K had no

apparent effect on the prothrombin, as it continued to diminish. On October 5 a generalized purpuric rash developed. A transfusion of 500 cc of fresh citrated blood was given on October 6 in an effort to relieve the anemia and to increase the prothrombin, but the patient gradually grew worse. The edema and ascites increased, the purpura became more widespread, and the prothrombin level fell to 24 per cent of normal. An attempt to give human wet plasma was made, but after 230 cc had been introduced there was a severe reaction, characterized by chill, urticaria and fever. A transfusion of 500 cc of reenforced whole citrated blood was given later in the day, and, as expected, it had no effect on the purpuric rash but increased the prothrombin from 24 to 37 per cent of normal. Table 3 lists the transfusions and determinations of prothrombin.

On October 12, the prothrombin content fell to 18 per cent of normal and the patient had several large hemorrhages in the mouth, nose, stomach, rectum and subcutaneous tissues. A Miller-Abbott tube was in the stomach when the bleeding occurred. The tube was left in place, and the patient was given 500 cc of fortified blood. Within two hours there was a great diminution in the amount of blood drained from the stomach, and in four hours the fluid was almost normal in color and the hemoglobin content reduced from 18 per cent to 0. The bleeding from the other areas had



ceased, and the prothrombin level was up to 38 per cent of normal in four hours

Another fortified transfusion was started the following day, but after 100 cc of blood had run in there was a reaction similar to that seen following the transfusion of plasma. Fifty per cent diluted plasma given intravenously was tried that afternoon, but after 2 cc had been introduced there was an even more severe reaction than previously, with extreme difficulty in breathing, giant urticaria and a temperature of 107 F. This bottle of plasma was carefully examined and found sterile, and it failed to produce a reaction in an animal.

On October 14, a fortified transfusion was slowly given, without reaction, and increased the prothrombin

CASE 4—C H L, a 29 year old white man, was admitted to the hospital May 21, 1942, with complaint of nausea, vomiting, drowsiness and jaundice for the past week. His general health had been excellent until this illness. He had never used tobacco or alcohol in any form, and he had not had any disease of the biliary system.

Physical examination revealed a well nourished and extremely well developed man, who did not appear ill. There was some icterus of the scleras and mucous membranes, but the skin was fair and smooth, without yellow color. The heart and lungs were essentially normal, the abdomen was moderately distended, and there was some epigastric tenderness. The liver and spleen were felt to be of normal size by palpation.

TABLE 3—Effects of Transfusions on Bleeding and on Prothrombin Level in Case 3

Date	Amount of Reenforced Blood, Cc	Amount of Whole Blood, Cc	Prothrombin Before Transfusion, Percentage of Normal	Prothrombin After Transfusion, Percentage of Normal	Time Between Transfusion and Determination of Prothrombin, Hr	Effect on Bleeding in 24 Hours	Bleeding Tendency
9/30/42			46*	38*	10	0	No bleeding
10/ 6/42		500	32	42*	10	0	Purpura
10/ 8/42	500		24*	46*	4	0	Purpura
10/ 9/42	500			58*	18	0	Purpura
10/10/42	500			18	4		
10/12/42	500 p m	500 a m	18	38	4	Ceased	Generalized hemorrhages
10/13/42				46	24	0	No bleeding
10/14/42	500		26	42	4	0	No bleeding

\* Determined by Quick method (other values obtained by the Smith "bedside" technique)

TABLE 4—Effects of Transfusions on Bleeding and on Prothrombin Level in Case 4

Date	Amount of Reenforced Blood, Cc	Amount of Whole Blood, Cc	Prothrombin Before Transfusion, Percentage of Normal	Prothrombin After Transfusion, Percentage of Normal	Time Between Transfusion and Determination of Prothrombin, Hr	Effect on Bleeding in 24 Hours	Bleeding Tendency
6/22/42		500				Ceased	Large purpuric areas on skin
7/11/42		500	16	19	8	0	Subcutaneous hemorrhages and hematuria
7/12/42	300		17	38	4	Ceased	Subcutaneous hemorrhages and hematuria
7/15/42		500	12	14	4	0	Subcutaneous, oral and renal hemorrhages
7/15/42	500		14*	43*	12	Ceased	Subcutaneous oral and renal hemorrhages
7/16/42	500		43*	58*	24	0	0
7/17/42	500		58*	70*	26	0	0
7/18/42	500		70	75	24	0	0
7/23/42	500		15*	36	4	Ceased	Oral and subcutaneous hemorrhages
7/23/42				42	22	0	0
7/24/42	500		42	58	26	0	0
7/30/42	500		20	38	8	0	0

\* Determined by Quick method (other values obtained by the Smith "bedside" technique)

from 26 per cent to 42 per cent of normal. Although the bleeding tendency was controlled, the patient rapidly grew worse, and he died October 15 from hepatic failure and generalized anasarca.

Autopsy showed generalized anasarca and several old large subcutaneous hemorrhages. There were severe pulmonary edema and numerous areas of pneumonia. The abdomen showed moderate ascites, the gastrointestinal tract was greatly distended, and there was evidence of old hemorrhages in the stomach, colon and rectum. The pathologists estimated these hemorrhages all to be about the same age. The spleen was about ten times the normal size. The liver was nodular, larger than normal and firm. Grossly, the liver resembled atrophic cirrhosis, and this was verified to some extent on microscopic examination, except that there was practically complete atrophy of the hepatic cells

and percussion. The hemoglobin content was 90 per cent, the red blood cell count 4,600,000, the white blood cell count 5,150, the Kahn reaction negative and the icteric index 56. The urine was normal except for bile, and the stools were light but contained some bile.

The patient gradually grew worse, and by June 15 the icteric index had increased to 200, the liver had enlarged to 5 cm below the costal margin, and the patient was drowsy. A week later, on June 22, large purpuric areas developed over his entire body, with clotting time of eight minutes and platelet count of 210,000. The patient was given 500 cc of whole blood, and 5 mg of menadione intravenously, and by the following day the clotting time was normal and the rash had disappeared. Table 4 lists the transfusions and the prothrombin values.

By June 25, the liver was palpable 10 cm below the costal margin, the spleen was easily felt and a



small amount of fluid had collected in the abdomen. The ascites increased over a period of eleven days and then rapidly receded after large amounts of plasma were given. On July 11, while the patient was receiving adequate amounts of vitamin K intramuscularly, hematuria and a fine purpuric rash appeared and large subcutaneous hemorrhages developed on minimal trauma of the skin. The clotting time was ten minutes and the prothrombin content 16 per cent of normal. Transfusion of 500 cc of fresh whole blood and 1,000 cc of wet plasma lowered the clotting time to eight and one-half minutes and elevated the prothrombin level to 19 per cent but had no effect on the hemorrhagic tendencies. A 300 cc transfusion on July 12, from a donor who had received 12 mg of menadione, caused a prompt elevation of the prothrombin to 38 per cent of normal in four hours, and the hemorrhagic tendencies subsided within twenty-four hours, but there was no effect on the purpuric rash. The fortified transfusions were not continued, but vitamin K and plasma were given daily. On July 15, the prothrombin fell to 12 per cent, and there was a recurrence of subcutaneous and renal bleeding and, in addition, oral bleeding. Again the patient failed to respond to 500 cc of whole blood. Because of the extensive bleeding 500 cc of fortified blood was given, and there was a rapid response, with elevation of the prothrombin to 43 per cent of normal. Daily fortified transfusions were given the following three days, and on July 18 the prothrombin content was 75 per cent of normal. Administration of vitamin K was discontinued, as it was felt that it was of little or no value. On July 23, there was a recurrence of the oral and subcutaneous bleeding, the prothrombin being reduced to 15 per cent of normal. Again there was definite response to a 500 cc fortified transfusion, the prothrombin level rising to 42 per cent of normal within twenty-four hours. From this time on, the patient was given fortified transfusions when the prothrombin content fell below 20 per cent, which was usually about every three days, and there were no further hemorrhagic tendencies. A month later the patient developed the rather typical lesions of disseminated lupus erythematosus, and their nature was confirmed by biopsy. The liver, which at one time had been large, was now palpable immediately below the costal margin and was somewhat firmer than normal. The spleen was easily palpable and rather soft.

#### COMMENT

It is generally accepted that the liver has an enormous functional, as well as tissue, reserve, and that it rarely works at full capacity. Also, the liver has marked regenerative abilities, and it is only in the presence of acute injury or of prolonged chronic disease that sufficient tissue is destroyed to diminish the reserve and produce evidence of hepatic deficiency. If the hepatic insufficiency is severe enough, death may occur. Deaths in such circumstances fall under two general heads, namely, "hemorrhagic death" and "liver death."

Transfusion of blood fortified by administration of vitamin K to the donors was used as a temporary aid in controlling hemorrhage in 4 cases of severe acute damage to the liver. The small number of cases, variations in the preparation of the donors and the necessity of using two

different technics in determinations of prothrombin prevent any specific conclusion, but the evidence obtained indicates that the method may have definite value in preventing immediate "hemorrhagic death" or in controlling hemorrhage until there has been regeneration of sufficient hepatic tissue for essential functions. From the tables it will be noted that in several instances the prothrombin times are inconsistent and that the increase in prothrombin varied from patient to patient and from transfusion to transfusion. It was unfortunate that conditions beyond our control prevented determination of the prothrombin time whenever desired and that the determinations could not be made by the same method. It will also be noted from the tables that the transfusion of normal whole blood failed to give the expected 10 per cent rise in the prothrombin level. On careful analysis it will be noted that the maximum elevation of prothrombin in the blood usually occurred within twenty-four hours but that in the instances in which the liver was still badly damaged there was usually a decline during the second twenty-four hours. A striking feature of case 1 was the regularity with which the bleeding ceased between one hundred and twenty and one hundred and forty minutes after transfusion on all occasions. In cases 3 and 4, fortified transfusions, as well as regular transfusions, had no effect on a minute purpuric rash but controlled hemorrhages in the skin and subcutaneous tissues.

Determination of the optimum amount of vitamin K and of the period of time required for its utilization by the donor requires further work, but in general it may be stated that 6 to 10 mg of menadione given intramuscularly during the twenty-four hours before a transfusion will work satisfactorily. The evidence suggests that vitamin K stimulates the formation of prothrombin or of one of its precursors in the blood of the donor in abnormally large amounts, which can be utilized by the recipient. The substance formed is probably the same as or similar to that formed from vitamin K by the pregnant mother, which passes through the placenta into the fetus to stimulate formation of prothrombin.

#### SUMMARY

Five cases of acute yellow atrophy of the liver with hemorrhagic tendencies occurred in a series of 663 cases of intrahepatic jaundice. Four of the patients were given transfusions of blood from donors who had received vitamin K, with remarkable effect in controlling the bleeding tendencies. The results suggest that this method deserves further study and investigation.

# FLUID DYNAMICS IN CHRONIC CONGESTIVE HEART FAILURE

AN INTERPRETATION OF THE MECHANISMS PRODUCING THE EDEMA, INCREASED  
PLASMA VOLUME AND ELEVATED VENOUS PRESSURE IN CERTAIN PATIENTS  
WITH PROLONGED CONGESTIVE FAILURE

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Many theories have been formulated in an attempt to explain the clinical features and laboratory findings of chronic congestive heart failure. Today most medical students are taught that the venous pressure becomes elevated because blood is dammed up in the venous system when the ability of the heart to pump blood forward is impaired. Edema is said to occur primarily as a result of this increase in venous pressure, with increased capillary permeability and decreased colloid osmotic pressure of the blood as contributing factors. Nevertheless, there are many clinical and experimental observations which are not consistent with this usually accepted theory. The purpose of this presentation is to summarize these objections and to offer a more satisfactory explanation of the physiologic abnormalities producing the edema, the increased blood volume and the elevated venous pressure of certain patients with congestive heart failure. Few new data are presented, but the findings of other investigators are correlated to explain the observed alteration in the fluid dynamics of chronic cardiac failure.

Most observations relating to cardiac failure have been made on patients who were regaining compensation, rather than when the congestive failure was developing. If the latter condition is observed it can be seen that in certain patients an accumulation of extracellular fluid, evidenced by an increase in weight, occurs before any increase in the venous pressure is demonstrable. Associated with this gain in weight there is a proportionate increase in the blood volume, and only as a later manifestation does the venous pressure become elevated. These facts are not compatible with the usual description of the mechanism of congestive heart failure. The following cases demonstrate the course of events in patients with cardiac disease in whom decompensation has been precipitated by the administration of large

amounts of sodium chloride while they were under observation in the hospital.

**CASE 1**—A 50 year old Negro was admitted to the Grady Hospital on Sept 9, 1942. In 1939 he first noted dyspnea, edema of the ankles and other symptoms of congestive heart failure. He was admitted to the hospital several times because of these symptoms, and the diagnosis of arteriosclerotic and hypertensive heart disease was made. He improved while in the hospital, but later, despite a sedentary existence and the administration of digitalis and occasional diuretics, his symptoms recurred. On admission he was markedly orthopneic and there was massive edema below the level of the heart. The veins of his neck were greatly distended. The heart was enlarged, the rhythm was regular, and there was a rough apical systolic murmur. The arterial pressure was 140 mm of mercury systolic and 100 diastolic. There were numerous râles at the bases of both lungs. Examination of the blood and urine showed no abnormalities.

During the early part of his hospital course he was given a diet with low salt content and was treated with digitalis, ammonium chloride and frequent injections of a mercurial diuretic. The fluid intake was not restricted. Within two weeks his weight fell from 71 to 52 Kg, and dyspnea and orthopnea were no longer present.

On September 24 salt was added to his diet, and in addition he received 12 Gm of sodium chloride per day. His fluid intake and dosage of digitalis were not changed, but the use of diuretics was discontinued. With this change in regimen his weight immediately began to increase, as shown in table 1. In addition, there was an increase in plasma volume as measured by the dye method,<sup>1</sup> this being evidenced also by the falling plasma protein concentration and the decreased hematocrit readings. During the first part of this period his venous pressure was normal. It later rose slightly above the control readings, though it remained well within the normal range. The only change noted by the patient was slight orthopnea toward the end of the test period. Accordingly, the original scheme of therapy was again employed, and by October 24 he was able to leave the hospital without symptoms or signs of decompensation.

This patient remained well compensated as long as his salt intake was limited and diuretics

1 Gibson, J G, and Evans, W A, Jr. Clinical Studies of Blood Volume. I. Clinical Application of Method Employing Azo Dye "Evans Blue," and the Spectrophotometer, *J Clin Investigation* 16:301 (May) 1937.

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were administered, but when the use of diuretics was discontinued and salt was added his weight increased and there was an associated increase in plasma volume. The venous pressure rose slightly but stayed within normal limits. He remained in bed throughout the test period. The important fact is that the retention of water and hemodilution occurred while the venous pressure was normal

The fluid intake was not restricted at any time. On August 3 her regimen was altered, as in the previous case, by addition of salt to her diet, and in addition she received 12 Gm of sodium chloride daily. She remained in bed. Digitalis was continued, but no further diuretics were given. With this regimen her weight increased steadily and there was a parallel increase in plasma volume, but the venous pressure remained normal. Associated with the increase in the plasma volume there was hemodilution, indicated by a diminished hematocrit reading and a lowered plasma

TABLE 1—Summary of Observations on Case 1

Date, 1942	Weight, Kg	Plasma Volume, Cc	Plasma Protein Concentration, Gm per 100 Cc	Total Circulating Protein, Gm	Hematocrit Reading	Venous Pressure, Mm Water	Comments
September 15	56.5	3,800	6.4	243	45	100	During period of diuresis, low salt intake
22	52.2	2,900	7.4	214	55	40	No edema or orthopnea
23	51.9	3,000	7.2	216	54	40	
24	52.0						Salt intake increased, diuretics omitted
26	52.6						
28	53.1	3,400	6.6	224	49	50	
30	53.3						
October 3	54.9	3,500	6.4	224	46	50	
6	55.3		6.4		44	80	Slight orthopnea
8	56.3	3,800	6.1	232	43	80	

TABLE 2—Summary of Observations on Case 2

Date, 1942	Weight, Kg	Plasma Volume, Cc	Plasma Protein Concentration, Gm per 100 Cc	Total Circulating Protein, Gm	Hematocrit Reading	Venous Pressure, Mm Water	Comments
July 29	45.0						Low salt diet
31	46.3						
August 3	45.0	2,320	6.9	160	43	40	Salt intake increased, diuretics omitted
4	46.3						
5	47.6	2,700	6.4	173	38	40	
6	50.0						
7	52.0		6.0		36	150	
8	53.1	4,070	6.2	252	35	150	
9							
10							
11	53.7	3,740	6.4	240	32	160	
13	57.8						Edema and orthopnea
14	58.3				34	170	
15	58.5	3,600	6.3	228	32	175	
17	57.2						
20	56.7	4,000	6.4	256	31	160	

CASE 2—A 42 year old Negro woman was admitted to the Grady Hospital on March 23, 1942. In 1933 she had symptoms suggestive of acute rheumatic fever, and in 1939 she first had dyspnea and edema. Because of these symptoms she was repeatedly admitted to the hospital, where she would improve when digitalized and maintained at complete rest in bed. A slight increase in her activity was sufficient to precipitate decompensation. On this admission physical examination showed edema, distended veins in the neck and cardiac enlargement. There were a moderate systolic murmur and a rumbling diastolic murmur at the apex. Examination of the blood and urine showed no abnormalities. A diagnosis of rheumatic heart disease with mitral stenosis and congestive failure was made.

After treatment with diuretics and a diet with low salt content, her weight became stationary near 45 Kg

protein concentration. The data are given in table 2. The total amount of circulating protein was increased. On August 7, after she had gained 7 Kg, the venous pressure became elevated. In the following days edema appeared and the edge of the liver decreased, and on August 13 she first complained of dyspnea at rest. On August 25 the original regimen was reinstituted, after which she slowly regained compensation.

In this case, as in case 1, congestive failure was produced by the ingestion of sodium chloride. During this period no diuretic was administered. Observe the sequence of the changes. First, there was a gain in weight, which other investigators have shown is accompanied by retention of sodium chloride. This gain in

weight meant that the amount of extracellular fluid was increased. Associated with this there was a rise in plasma volume, as shown directly by the dye technic and indirectly by the fall in the hematocrit reading. As in case 1, increase in body weight and in the plasma volume preceded the rise in venous pressure.

It has been demonstrated that it is difficult to remove all the excess extracellular fluid from patients with congestive heart failure.<sup>2</sup> The extracellular fluid content remains abnormally high even when there is no longer any demonstrable edema. If such patients who are not completely compensated are given excess salt, the venous pressure may rise simultaneously with the gain in weight and the increase in plasma volume.

Patients with hypertension, aortic insufficiency and arteriosclerosis of the coronary vessels usually begin to have dyspnea before their venous pressure rises. Many of them become orthopneic while the systemic venous pressure is still normal. It is easy to show that these patients have an abnormally large volume of extracellular fluid, though many of them have little demonstrable edema. When placed in bed and treated for congestive failure, they rapidly lose 2 to 10 Kg in weight. Again, this is evidence that retention of salt and water has preceded the increase in systemic venous pressure. It is a frequent clinical observation that patients with repeated attacks of paroxysmal nocturnal dyspnea but without obvious edema often show striking improvement when the urinary output is increased by the use of a mercurial diuretic.<sup>3</sup>

Consideration of the observations on these patients, as well as the similar results of other investigators, reveals that there are three basic questions to be answered. First, why does the patient with chronic cardiac insufficiency retain salt and water—in other words, acquire edema—instead of having a normal diuresis of these substances? Second, how does such a patient acquire and maintain the abnormally large plasma volume that is so characteristic of congestive failure? Third, why does the elevation in venous pressure occur, and what is its relation to the other findings? Solution of these problems would contribute to a great extent toward a complete understanding of the pathogenesis of congestive failure.

2 Seymour, W. B., Pritchard, W. H., Longley, L. P., and Hayman, J. M., Jr. Cardiac Output, Blood and Interstitial Fluid Volumes, Total Circulating Serum Protein and Kidney Function During Cardiac Failure and After Improvement, *J. Clin. Investigation* **21**: 229 (March) 1942.

3 Fishberg, A. M. Heart Failure, ed 2, Philadelphia, Lea & Febiger, 1940.

## RETENTION OF SALT AND WATER

The problem of formation of edema in cardiac failure has received considerable attention, but at the present time none of the usually accepted theories regarding it is entirely satisfactory. It is well known that before edema is obvious there is usually an asymptomatic gain of several pounds in weight, indicating that the accumulation of an excessive amount of extracellular fluid has begun. Since this fluid is principally a solution of sodium chloride in water, the basic problem is to explain the abnormal retention of these substances. Much of the difficulty in studying edema formation is due to ignorance of the mechanisms controlling the amount of extracellular fluid normally present in the body. For instance, the diuresis that normally follows the ingestion of an isotonic saline solution has never been adequately explained.

The retention of salt and water may result primarily from disturbance in function of the kidney, either renal in origin or the result of hormonal influences. This failure to excrete salt and water normally causes a secondary increase in the quantity of extracellular fluid. On the other hand, the retention of salt and water may result primarily from an increase in the extracellular fluid content of the body. In nutritional edema water and salt are retained because the fluid passes from the blood stream to the tissues in consequence of the lowering of the osmotic pressure of the plasma proteins. When the permeability of the capillaries is increased, as in burned areas, fluid likewise passes from the blood stream to the tissues. When the venous pressure is raised because of obstruction to the venous outflow from a part, the volume of extracellular fluid in the part is increased because of the rise in capillary pressure. Those conditions which produce a primary increase in extracellular fluid content of the tissues cause in turn a secondary decrease in urinary output which is not dependent on a change in renal function. The venous pressure theory of the mechanism of cardiac edema postulates that the decreased urinary output is secondary to the increased extracellular fluid content of the tissues which results from the rise in venous and capillary pressures. The fact that retention of salt and water occurs in some patients with cardiac failure before the venous pressure becomes elevated and persists for a considerable period after the venous pressure has returned to normal suggests that the elevation of the venous pressure may not be the primary factor in the formation of cardiac edema.

Increased permeability of the capillaries to protein has been suggested as the causative fac-

to in the development of the edema of congestive failure. This belief is strengthened by the observation in animals that a diminished circulation, with its resultant anoxemia, increases capillary permeability.<sup>4</sup> If increased capillary permeability were present, one would expect that the edema fluid would contain large amounts of protein, but repeated investigations have shown that the protein content of cardiac edema fluid is low, usually less than 0.5 Gm per hundred cubic centimeters.<sup>5</sup> We have obtained additional evidence that anoxemia is not an important factor by examining edema fluid obtained from patients with severe emphysema and long-standing anoxemia. The edema fluid of 4 such patients contained from 0.1 to 0.4 Gm of protein. These patients, who had severe and long-standing anoxemia with pronounced arterial oxygen unsaturation (40 to 60 per cent), had a much greater degree of anoxemia than the average patient with heart failure, yet they gave no evidence of increased permeability.

Smirk<sup>6</sup> has suggested that the capillaries in cardiac failure, while not abnormally permeable to colloids, allow crystalloids to pass with greater ease and rapidity than normal. Thus, with a given increase in venous pressure he found that in patients with congestive failure more edema was produced during a test period than in normal subjects. If the capillaries did allow crystalloids to pass more rapidly than normal, edema would, indeed, form more quickly, but it is difficult to see how this time factor could in the end be significant, because in congestive failure edema usually develops over a period of days and weeks and does not have to take place in any given period of time.

Repeated observations on patients with congestive failure have shown that the plasma protein concentration and therefore the colloid osmotic pressure are often somewhat below normal. In certain instances, particularly in cases of constrictive pericarditis, the values are definitely low and contribute appreciably to formation of edema. However, since in many patients the plasma protein concentration is normal and since in the majority it is not greatly lowered, a decrease in plasma protein concentration cannot

be the primary factor responsible for cardiac edema.<sup>3</sup>

The experiments reported by McMaster<sup>7</sup> have suggested that a faulty lymphatic return may be a factor in the development of cardiac edema. The protein content of the edema fluid gives evidence against this as the cause of edema formation in congestive failure. With lymphatic obstruction one finds a very high protein concentration in the edema fluid, whereas low values are found in cardiac edema.<sup>8</sup>

From this discussion it can be seen that the edema of congestive failure cannot be explained by the usually accepted mechanisms of formation of edema, in which the retention of salt and water results primarily from an excess accumulation of fluid in the tissues with a secondary decrease in urinary output. It appears that the increase in the volume of extracellular fluid results from the fact that the kidneys do not excrete salt and water normally. On a theoretic basis, if either the sodium or the chloride ion or water were retained primarily, the body would retain the others in order to maintain a normal ionic balance. Schroeder,<sup>9</sup> Proger, Ginsberg and Magendantz<sup>10</sup> and Schemm<sup>11</sup> have shown that with an extremely low intake of sodium chloride water is not retained by the patient with cardiac insufficiency, but that even the amounts of sodium chloride in the average diet are sufficient to allow for considerable retention of water. It is a common observation that salts such as potassium chloride and ammonium chloride fail to cause retention of water and are even diuretic.<sup>12</sup> On the other hand, sodium bicarbonate acts in almost the same way as sodium chloride in causing retention of water. Quantitative interpretation of these data is not possible because of the accompanying alkalosis and acidosis, but

7 McMaster, P. D. The Lymphatics and Lymph Flow in the Edematous Skin of Human Beings with Cardiac and Renal Disease, *J. Exper. Med.* **65** 373 (March) 1937.

8 Drinker, C. K., and Yoffey, J. M. Lymphatics, Lymph, and Lymphoid Tissue, Cambridge, Mass., Harvard University Press, 1941.

9 Schroeder, H. A. Studies on Congestive Heart Failure. I. The Importance of Restriction of Salt as Compared to Water, *Am. Heart J.* **22** 141 (Aug) 1941.

10 Proger, S., Ginsberg, E., and Magendantz, H. Effects of Ingestion of Excessive Amounts of Sodium Chloride and Water on Patients with Heart Disease, *Am. Heart J.* **23** 555 (April) 1942.

11 Schemm, F. R. A High Fluid Intake in the Management of Edema, Especially Cardiac Edema. I. The Details and Basis of the Regime, *Ann. Int. Med.* **17** 952 (Dec) 1942.

12 Goodman, L., and Gilman, A. The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941.

4 Landis, E. M. Micro Injection Studies of Capillary Permeability. III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to Plasma Proteins, *Am. J. Physiol.* **83** 528 (Jan) 1928.

5 Bramkamp, R. G. The Protein Content of Subcutaneous Edema Fluid in Heart Disease, *J. Clin. Investigation* **14** 34 (Jan) 1935.

6 Smirk, F. H. Observations on the Causes of Oedema in Congestive Heart Failure, *Clin. Sc.* **2** 317 (Dec) 1936.

they point toward the importance of the sodium ion as the primary factor in the retention of salt and water

The retention of sodium could occur as the result of a primary renal abnormality or it could be the result of some hormonal influence mediated by the kidney. It has been suggested that an excess of adrenal cortical hormone could cause the observed retention of sodium<sup>13</sup>. At the present time there is no additional reason to suspect that an excessive amount of this hormone is present in subjects with cardiac failure. It is quite possible that altered circulatory dynamics in the kidney could lead to retention of salt. The kidney receives a large proportion of the cardiac output at rest<sup>14</sup>, therefore, it appears quite possible that pronounced alterations in renal circulation occur with the diminished cardiac output in cardiac failure. This problem is being investigated further in this laboratory.

The common denominator in all instances of congestive failure is impaired cardiac function. In most patients cardiac failure first develops while they are ambulatory and is improved by rest. This indicates that although the diseased heart may supply the needs of the body at rest, it cannot increase its output to meet the demands of an active life. Determinations of cardiac output of patients with cardiac failure are usually done under basal conditions, so one might predict their failure to demonstrate any marked differences between the output of normal subjects and that of patients with cardiac failure. The evidence at present points to the fact that in congestive failure the cardiac output is inadequate to meet the demands of the patient's daily life, and, as a result of this, the kidneys are no longer able to excrete salt in a normal manner. The retention of salt leads to the secondary retention of water. This accounts for the fact that in patients with severe decompensation, in whom the cardiac output is inadequate even at rest, the signs of congestive failure may be precipitated at will by withholding diuretics and increasing the intake of salt. As far as can be determined, increasing and decreasing the salt intake of these patients induces and relieves the symptoms of congestive failure without any corresponding change in cardiac output. The question remains unanswered as to how the decreased cardiac output affects the ability of the kidney to excrete salt. It may be related to a decreased

renal blood flow, or it may be due to some endocrine disturbance which produces an increased retention of sodium by the kidneys.

#### INCREASED BLOOD VOLUME

For many years clinicians have known that congestive heart failure is accompanied by increased blood volume, but the mechanism of the rise has never been explained in a satisfactory manner<sup>15</sup>. It has been found to be an increase primarily in the plasma volume, although there also may be an increase in red cell volume.

In a normal resting subject with a constant arterial pressure and a constant volume of circulating red cells, the size of the plasma volume can be varied by changing (1) the amount of circulating plasma protein, (2) the capillary pressure or (3) the extracellular fluid volume.

If the quantity of circulating protein is increased by the injection of a concentrated protein solution, fluid enters the blood stream and the plasma volume is increased for a time<sup>16</sup>. The body then removes protein from the plasma, the fluid reenters the tissues and the plasma volume returns to normal. If protein is removed from the blood stream, the plasma volume decreases rapidly even though the fluid removed with the protein is replaced by an equal quantity of saline solution<sup>17</sup>. The body then adds protein to the blood stream, fluid can now be retained in the plasma in normal quantity, and the plasma volume returns to the control level.

An increase in venous pressure causes a rise in capillary pressure, with the result that fluid leaves the blood stream. In the normal subject a rise in venous pressure causes some degree of hemoconcentration.

An increase or decrease in the volume of extracellular fluid produces a corresponding change in the plasma volume. If the quantity of extracellular fluid is lowered by dehydration, the plasma volume becomes smaller<sup>18</sup>. This

15 (a) Gibson, J. G., and Evans, W. A., Jr. Clinical Studies of the Blood Volume. III. Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, *J. Clin. Investigation* **16** 851 (Nov.) 1937. (b) Seymour and others.<sup>2</sup>

16 Freeman, N. E., and Wallace, W. M. Effect of Concentrated Serum on Plasma Volume and Serum Protein Concentration, *Am. J. Physiol.* **124** 791 (Dec.) 1938.

17 Ebert, R. V., Stead, E. A., Jr., and Gibson, J. G. Response of Normal Subjects to Acute Blood Loss, *Arch. Int. Med.* **68** 578 (Sept.) 1941.

18 Gibson, J. G., and Kopp, I. Studies in the Physiology of Artificial Fever. I. Changes in the Blood Volume and Water Balance, *J. Clin. Investigation* **17** 219 (May) 1938.

13 Schroeder, H. A., and Fitcher, P. H. Studies on Congestive Heart Failure. II. Impaired Excretion of Sodium Chloride, *Am. J. Med. Sc.* **204** 52 (July) 1942.

14 Smith, H. W. Studies in the Physiology of the Kidney. Porter Lectures, University of Kansas, Lawrence, Kan., University Extension Division, 1939, series 9.



decrease in volume occurs even though the protein concentration is increased. In other words, in the presence of a decrease in extracellular fluid it takes a greater than normal quantity of circulating plasma protein to maintain a normal plasma volume. When the volume of extracellular fluid is increased by the administration of desoxycorticosterone, the plasma volume tends to increase.<sup>19</sup> In pregnancy both the plasma volume and the amount of extracellular fluid are increased.<sup>20</sup> The relationship between the extracellular fluid volume and the plasma volume has been studied for patients with nephrosis and also for dogs. The patient with nephrosis maintains an adequate plasma volume with a small amount of circulating protein. A similar amount of circulating protein in a person with a normal extracellular fluid volume would result in a plasma volume too small to maintain a normal circulation. The most striking difference is that the patient with nephrosis has an increase in extracellular fluid volume. It has been found that in dogs in which the total circulating protein has been reduced by from 30 to 60 per cent the plasma volume can still be maintained at a normal level by markedly increasing the extracellular fluid volume.<sup>21</sup>

In acute experiments changes in the volume of the extracellular fluid produce parallel changes in the pressure of the extracellular fluid, and it is probable that it is the pressure rather than the volume of the extracellular fluid which is important in determining the plasma volume. In chronic conditions in which the elasticity of the tissue is decreased by loss of weight or by previous stretching of the tissues by edema, large quantities of extracellular fluid must accumulate before there is an appreciable rise in the pressure of the extracellular fluid. The system is variable because of the tendency of the tissues to stretch. For this reason, at times the volume of extracellular fluid must be slowly increased in order to maintain a constantly elevated extracellular fluid pressure.

These observations may be applied to the patients described here with congestive failure.

19 Thorn, G. W., and Emmerson, K., Jr. The Role of Gonadal and Adrenal Cortical Hormones in the Production of Edema, *Ann Int Med* **14** 757 (Nov) 1940.

20 Thomson, K. J., Hirscheimer, A., Gibson, J. G., and Evans, W. A., Jr. Studies on the Circulation in Pregnancy. III. Blood Volume Changes in Normal Pregnant Women, *Am J Obst & Gynec* **36** 48 (July) 1938.

21 Warren, J. V., Merrill, A. J., and Stead, E. A., Jr. The Role of the Extracellular Fluid in the Maintenance of a Normal Plasma Volume, *J Clin Investigation* **22** 635 (Sept) 1943.

The increase in extracellular fluid resulting from the retention of salt and water appears as the earliest manifestation of cardiac insufficiency, and it offers an adequate explanation of the increase in blood volume which has been noted. As may be seen in the many recorded observations of congestive failure, the plasma volume and the extracellular fluid volume increase and decrease concordantly. The situation is similar to that observed with the retention of salt and water resulting from the administration of adrenal cortical hormone.<sup>19</sup> The relation of the increase in plasma volume to the changes in venous pressure will be discussed later, but since the increased blood volume occurs before a change in venous pressure, the increase in the latter is obviously not a causative factor. The changes in plasma protein are more complex. When hemodilution occurs because of the retention of salt and water, the lowering of the concentration of the plasma proteins serves as a stimulus for the production of more plasma protein. Thus, as the plasma volume increases because of the increase in the salt and water content of the body, the quantity of circulating protein also usually increases. When the fluid content of the body is decreased by therapy and the plasma volume returns to normal, the body removes protein from the plasma and the quantity of circulating protein also returns to normal.<sup>2</sup>

We may conclude, therefore, that the increase in plasma volume in congestive failure is one manifestation of the increase in the amount and pressure of the extracellular fluid which is caused by the defective excretion of salt and water.

#### INCREASED VENOUS PRESSURE

In chronic congestive failure of the type described here the increase in venous pressure occurs only after considerable salt and water have been retained and there has been a definite increase in the blood volume. We can now reevaluate the cause of the increased venous pressure in the light of these findings, but before doing so it may be well to enumerate the various factors that can elevate the venous pressure.

A clear distinction must be made between local increases in venous pressure because of gravity and a generalized increase throughout the venous system, such as is present in cardiac failure. In the normal subject the local venous pressure is elevated in any part which lies below the level of the heart. Thus, when a person is in the upright position the venous pressure is increased in the parts of the body below the level of the heart. The venous pressure in the great veins of the thorax at heart



level, however, is not elevated. In the patient with elevated venous pressure from cardiac failure, the venous pressure in the great veins of the thorax at heart level is elevated, usually about 10 to 20 cm of water, with the subject in either the recumbent or the upright position. When this person stands, the pressure in the veins of his ankles is the sum of that in the great veins of the chest and that produced by gravity. It is important to remember that the increased pressure produced by gravity far exceeds that caused by cardiac failure, so that in the upright position a short person with severe cardiac failure may have a lower venous pressure in the ankles than a tall person without cardiac failure.<sup>6</sup>

When the venous pressure in a part or organ is increased either by gravity or by compression of the veins draining the part, the vascular bed becomes distended and the venous pressure rises until the blood begins to flow past or around the point of obstruction. With the distention of the vascular bed, the part contains more blood than it did before the venous pressure was elevated. Compensatory reactions in other parts of the body supply the excess blood. The venous obstruction acts as a dam, and blood backs up behind the dam until the pressure becomes great enough to force the fluid past the point of obstruction. If it were not for the fact that extra blood can be drawn from other parts of the body and pumped into the part, the building of the dam would have a much less marked effect on the venous pressure. A dam placed across a stream makes a lake not with the water that is in the bed of the stream at the time the dam is built but with the water that is continually being added to the stream from above.

The elevation of the venous pressure, if allowed to continue, is followed by swelling of the part.<sup>22</sup> With any given increase in venous pressure the part swells rapidly at first, but after a time the rate of swelling markedly decreases. The increase in venous pressure causes a rise in capillary pressure, with the result that the mean capillary pressure exceeds the sum of the surrounding tissue pressure and the osmotic pressure of the proteins. Under these conditions water leaves the blood stream and enters the tissues. As the tissue pressure increases, the rate of swelling decreases, until in time the rise in mean capillary pressure is balanced by the increase in tissue pressure. If the blood in the part is examined during the

period of swelling, it will be found that the hematocrit reading and the protein concentration of the venous blood draining the area are rising—evidence of hemoconcentration.

The venous pressure in over one half of the body is increased by having the subject stand motionless. The increase in venous pressure in the part of the body below the heart causes fluid to leave the blood stream and enter the tissues. This loss of fluid takes place over such a wide area that not only is there hemoconcentration in the areas where the venous pressure is increased, but there is an easily demonstrable fall in the plasma volume.<sup>23</sup> This hemoconcentration can be partially prevented by the ingestion of large quantities of isotonic solution of sodium chloride, but in the normal subject it is difficult to maintain the plasma volume at the resting level. As fast as saline solution enters the blood stream, it is passed out into the tissues. In an experiment of this type it is worth noting that the urinary output is very small in spite of the large quantities of saline solution administered.<sup>24</sup>

A second way by which venous pressure can be elevated is by vasoconstriction with redistribution of blood in the vascular bed. An increase in venous tone may be produced by the action of a drug, such as epinephrine,<sup>25</sup> paredrinol sulfate ( $\alpha$ -N-dimethylparahydroxyphenethylamine sulfate)<sup>26</sup> or angiotonin,<sup>27</sup> or it may occur reflexly in response to decreased cardiac output. The increased venous pressure noted in cardiac tamponade is produced by a redistribution of blood within the vascular bed. As the pressure in the pericardial sac rises, the cardiac output falls and the arterial tree contains less blood. At the same time the tone of the venous bed is increased, either reflexly or as a result of a humoral mechanism set in motion by the decreased flow of blood to the kidney. The shift in blood from the arteries and the increase

23 Thompson, W. O., Thompson, P. K., and Dailey, M. E. Effect of Posture upon Composition and Volume of Blood in Man, *J. Clin. Investigation* 5:573 (June) 1928.

24 Stead, E. A., Jr., Ebert, R. V., and Warren, J. V. Unpublished data.

25 Wilkins, R. W., Weiss, S., and Haynes, F. W. The Effect of Epinephrine in Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* 17:41 (Jan) 1938.

26 Stead, E. A., Jr., and Kunkel, P. Mechanism of the Arterial Hypertension Induced by Paredrinol ( $\alpha$ -N-Dimethyl-p-Hydroxyphenethylamine), *J. Clin. Investigation* 18:439 (July) 1939.

27 Wilkins, R. W., and Duncan, C. N. Nature of the Arterial Hypertension Produced in Normal Subjects by Administration of Angiotonin, *J. Clin. Investigation* 20:721 (Nov) 1941.

22 Krogh, A., Landis, E. M., and Turner, A. H. The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood, *J. Clin. Investigation* 11:63 (Jan) 1932.

in venous tone cause a rise in venous pressure. This condition is not strictly analogous to the rise in pressure which occurs when a river is dammed up. The pressure back of the dam can rise to a great height because the quantity of the water back of the dam is steadily increased by the continuous flow of the river. This is the case when only a portion of the venous system is obstructed and the amount of blood distal to the point of obstruction can be rapidly increased by shifting blood from other parts of the body. However, if the entire venous system is obstructed, as it is in pericardial tamponade, the body has no immediate means of increasing the entire blood volume and thereby raising the venous pressure. Therefore, the rise in venous pressure in acute pericardial tamponade is not usually as great as in certain patients with chronic congestive failure—a condition in which the blood volume is increased.

The third way by which the venous pressure can be elevated is by increasing the blood volume. Studies of the relationship between the venous pressure and the blood volume in congestive failure have demonstrated that the plasma volume in a given patient increases when the venous pressure is elevated and that with therapy both the venous pressure and the plasma volume decrease as the circulation improves.<sup>15</sup> Starr<sup>26</sup> recorded the venous pressure immediately after death for patients with and without congestive failure. He found that the venous pressure in patients with cardiac failure remained elevated after death and concluded that the greater part of the rise in pressure was related to the increase in blood volume rather than to an actual change in the dynamics of a failing circulation.

In certain patients with chronic congestive failure the venous pressure increases only after there has been a considerable increase in blood volume, and the venous pressure returns to normal as the blood volume is reduced by therapy. The fact that the increase in venous pressure persists after death demonstrates that at least in certain patients the major portion of the rise in pressure cannot be the result of the increase in tone of the vascular bed. The same data show that the rise in venous pressure does not occur because blood is dammed up behind a failing right ventricle, for the increase in venous pressure persists in the absence of any pumping force from either the right or the left ventricle. It is concluded, therefore, that in chronic congestive failure the increase in the

volume of blood in the vascular bed is important in producing the rise in venous pressure, and that the increased pressure of extracellular fluid is the means by which the body is able to maintain the large plasma volume in spite of the high capillary pressure.

Local increases in venous pressure are of great importance in the placement of fluid which is retained in the body because of the failure of the kidneys to excrete the excess salt and water. It is common knowledge that in the ambulatory patient visible edema appears first about the ankles, where the venous pressure is the greatest. The following cases further illustrate the importance of the venous pressure as a determining factor in the placement of the retained fluid.

CASE 3—A 53 year old white woman was admitted to the hospital because of congestive failure due to rheumatic heart disease with mitral stenosis. There was, in addition, thrombosis of the left subclavian and axillary veins. She had moderate generalized edema, but there was massive edema of the left arm and hand, so that the overlying skin was tight and shiny. The venous pressure in the left antecubital vein was 340 mm of water and in the right 220 mm. Edema fluid obtained from both arms contained 0.1 Gm of protein per hundred cubic centimeters.

CASE 4—A 17 year old white girl was admitted to the hospital because of symptoms of congestive heart failure due to rheumatic heart disease with mitral stenosis and insufficiency. There was striking edema of the right arm and hand, but only moderate swelling elsewhere. The venous pressure in the right antecubital vein was 275 mm of water and in the left 150 mm. Edema fluid obtained from the left arm and leg contained 0.4 Gm of protein per hundred cubic centimeters.

In both of these patients there was local venous obstruction elevating the venous pressure in a part. In an otherwise normal person an increase in venous pressure of this magnitude does not produce such a degree of edema. Lymphatic block was not a factor, since the protein content of the edema fluid was low.<sup>8</sup> These patients had marked swelling because, in addition to the venous obstruction, they were actively retaining salt and water. Thus a slight increase in venous pressure, which would have caused little edema in a normal subject, produced marked local edema in the patient with cardiac failure. Although increased venous pressure is not the cause of the edema, it is an important conditioning mechanism. A similar situation may exist in the patient in whom increased pulmonary capillary pressure develops as a result of a momentary discrepancy in output from the right and left ventricles. In this manner, with retention of salt and water marked pulmonary edema may occur in a patient with relatively little edema elsewhere.

28 Starr, I, Jr. Role of the "Static Blood Pressure" in Abnormal Increments of Venous Pressure Especially in Heart Failure, *Am J M Sc* 199:40 (Jan) 1940

From the foregoing discussion it is clear that the generalized increase in venous pressure in chronic heart failure may be produced by the increase in blood volume. Local rises in venous pressure determine, however, the distribution of the excess extracellular fluid.

The mechanism described adequately accounts for the fact that in a case of chronic heart disease the venous pressure may be varied by changing the salt intake without altering the cardiac output. In acute heart failure the mechanism of the increase in venous pressure is more complicated. The mechanism of the rise in venous pressure in sudden acute heart failure is more closely related to that seen in acute pericardial tamponade than to the mechanism of retention of salt described for chronic congestive failure. The sharp decrease in cardiac output may cause an increase in vascular tone, either reflexly or by an outpouring of pressor substances from the kidneys. In addition, the arterial tree may contain less blood. Under these conditions the venous pressure may increase without a rise in blood volume. Strengthening of the heart by the use of digitalis may cause an increase in the output of the heart and a rapid decrease in venous pressure. In many patients the rise in venous pressure represents a summation of the effects of a large plasma volume and of a redistribution of blood secondary to an episode of more acute heart failure.

#### SUMMARY

The following hypothesis appears to offer a satisfactory explanation of the mechanism of cardiac edema. The common denominator of all patients with congestive failure is impaired cardiac function, which first fails to meet the demands of an active person. For some reason, as yet unexplained, these patients fail to excrete salt and water in a normal fashion. Retention of these substances in the body produces an increase in the quantity of extracellular fluid. Associated with this there is an increase in plasma volume. The hemodilution can be demonstrated by the fall in the hematocrit reading and in the concentration of plasma protein. The lowering of the concentration of plasma protein serves as a stimulus for production of such protein, and the total quantity circulating usually increases. In chronic congestive failure the blood volume finally becomes so large that the pressure in the vascular system is increased, and one says that the venous pressure is elevated. During the state of active retention of water the local changes in venous pressure in

certain parts of the body due to gravity act as directing factors in the placement of the excess fluid. Since the first signs of congestive failure normally appear while the patient is active, the high local venous pressure about the ankles predisposes to edema of those regions.

In the patient with advanced congestive failure there are increased extracellular fluid, increased plasma volume and high venous pressure. The patient is able to maintain such a state because the increased pressure in the capillary bed is balanced by an increase in tissue pressure brought about by large amounts of extracellular fluid. The final result may be modified by many factors. In the patient with tight skin, such as one frequently finds in Negroes, less retention of water is necessary to build up tissue pressure, and therefore such a person maintains a high venous pressure with less edema than does a patient with loose, flabby skin. In patients who have not lost weight, the quantity of extracellular fluid necessary to support a high plasma volume and a high venous pressure may be detected clinically only with difficulty.

Most patients with cardiac failure add protein to the blood stream in response to the hemodilution caused by the retention of salt and water so that the concentration of the plasma protein is almost normal and the total amount of circulating protein is increased. This enables them to maintain a large blood volume and a high venous pressure with a moderate increase in extracellular fluid pressure. When the plasma protein concentration is low, it takes a much greater increase in the quantity and pressure of the extracellular fluid to maintain a large enough plasma volume to produce a high venous pressure. In some patients the body does not add protein to the plasma to compensate for the hemodilution which is produced as the volume of the extracellular fluid increases. Such a situation is often observed in constrictive pericarditis.

In acute heart failure the increase in venous pressure may result from an increase in venous tone secondary to the marked decrease in cardiac output and from a redistribution of blood in the vascular bed. This may be caused by a humoral mechanism from the decreased renal blood flow, or it may be caused reflexly by the fall in cardiac output. These changes may be superimposed on the picture produced by chronic congestive failure.

#### CONCLUSIONS

1. Edema develops in chronic congestive failure because the kidneys do not excrete salt and water in a normal manner. This disturbance

in renal function is related to the decreased cardiac output and not to engorgement of the kidneys from an increased venous pressure, because the salt and water retention may occur before there is a rise in venous pressure

2 The increase in the plasma volume is a manifestation of the retention of salt and water. The resulting decrease in concentration of the plasma proteins usually stimulates production of plasma protein so that the total amount of circulating protein increases. The plasma volume is thus increased in size without a marked lowering of the osmotic pressure of the plasma proteins.

3 In due time the increase in the blood volume and the extracellular fluid volume causes a rise in the venous pressure. The osmotic pressure of the plasma proteins and the increased pres-

sure of the extracellular fluid provide the physical forces which enable the large plasma volume to be maintained in the presence of the high capillary pressure which results from the high venous pressure.

4 Local differences in venous pressure are of importance in that they determine the placement of the salt and water which are retained by the kidneys in congestive heart failure.

5 Other factors than retention of salt by the kidneys account for the rise in venous pressure in acute heart failure. In many patients the rise in venous pressure represents the summation of the effects of acute and chronic heart failure.

This investigation was carried out with the technical assistance of Rosamond Piotti, S B

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# ELECTROCARDIOGRAPHIC FEATURES ASSOCIATED WITH HYPERTHYROIDISM

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SAN FRANCISCO

Although the role of the heart in hyperthyroidism has attracted the attention of clinicians since Parry's description of exophthalmic goiter in 1825,<sup>1</sup> little accord has been reached as to the electrocardiographic manifestations of this condition. All observers agree that tachycardia and various arrhythmias may be attributed to the thyrotoxic state, but they do not agree on other findings.

In an attempt to determine what electrocardiographic abnormalities may be found in hyperthyroidism, a study was made of adult hyperthyroid patients observed in the thyroid clinic of the University of California Hospital from July 1935 through April 1942. Electrocardiograms were taken on 168 of 484 patients during the period of hyperthyroidism. All patients were seen by one observer (M H S), and all electrocardiograms were interpreted by another observer (F L C). In some cases the electrocardiographic studies were made because of the clinical diagnosis of thyrotoxic heart disease, especially as evidenced by arrhythmias, in others (when financial arrangements could be made), in order to determine what the electrocardiogram shows in cases of hyperthyroidism. In all cases the three standard leads were used. In 122 cases the precordial lead (IV-F) was used in addition.

The standards of normal established by Graybiel and White<sup>2</sup> were used, with the following additions:

1. The standards of auriculo-

Five tables originally prepared with this article are omitted from the ARCHIVES because of lack of space but will appear in the authors' reprints.

From the Department of Medicine, University of California Medical School, and the Thyroid Clinic and the Heart Clinic of the University of California Hospital.

1 Parry, C H. Diseases of the Heart. Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the Heart, in Collections from the Unpublished Medical Writings of the Late Caleb Hillier Parry, London, Underwood, 1825, vol 1, p 478, cited by Major, R H. Classic Descriptions of Disease, ed 2, Springfield, Ill., Charles C Thomas, Publisher, 1939.

2 Graybiel, A, and White, P D. Electrocardiography in Practice, Philadelphia, W B Saunders Company, 1941.

ventricular conduction time were taken from Ashman and Hull,<sup>3</sup> according to whom the maximum normal auriculoventricular conduction time varies inversely with age and heart rate.

2. Notching of the T waves in leads I and II was considered abnormal.<sup>4</sup>
3. Deviation of the axis to the left of approximately minus 35 to minus 55 degrees was considered abnormal.<sup>5</sup>
4. P waves of 0.12 second or more were considered abnormally wide,<sup>6</sup> but no record was considered abnormal on the basis of abnormal P waves alone.
5. T<sub>1</sub> was considered abnormally low if it was exceeded in height by T<sub>2</sub>, when the electrical axis was less than 0 degrees.<sup>5</sup>
6. T<sub>2</sub> was considered abnormally low if it was less than 2 mm in height (only 2 records were considered abnormal because the T<sub>2</sub> measurement was in the controversial range, between 1 and 2 mm).

Of the 168 patients for whom electrocardiograms were taken during the period of hyperthyroidism, 79 (or 47 per cent) had normal records and 89 (or 53 per cent) had abnormal records. Of those with abnormal records, 28 were excluded because conditions other than hyperthyroidism may have affected the electrocardiograms. These were hypertension in 15 cases, administration of digitalis, in 8 cases, disease of the coronary arteries, as evidenced by angina pectoris, by changes seen at autopsy or by preexisting bundle branch block in 4 cases, and rheumatic heart disease, in 1 case. In 2 cases of coexisting hypertension and hyperthyroidism auricular fibrillation disappeared after thyroidectomy, it therefore was ascribed to the hyperthyroidism. In 11 cases abnormalities of the T waves or of auriculoventricular conduction were discounted because digitalis had been administered, data on axis deviation and rhythm were included. In 61 cases (or 30 per cent) electrocardiographic abnormalities were

3 Ashman, R, and Hull, E. Essentials of Electrocardiography, New York, The Macmillan Company, 1937.

4 White, P D. Heart Disease, ed 2, New York, The Macmillan Company, 1938.

5 Katz, L N. Electrocardiography, Including an Atlas of Electrocardiograms, Philadelphia, Lea & Febiger, 1941.

observed for which hyperthyroidism was the only demonstrable cause. Of 140 cases of hyperthyroidism without other causes for electrocardiographic abnormalities, normal electrocardiograms were found in 79 (or 56 per cent) and abnormal records in 61 (or 44 per cent).

Evaluation of the electrocardiographic abnormalities attributed to hyperthyroidism in previously reported series of cases has been difficult because other causes were not eliminated and patients of all age groups were included. Since older patients may have electrocardiographic abnormalities as the only demonstrable evidence of degenerative heart disease, we divided the patients in our series into arbitrary age groups. The age group from 14 to 40 years consisted of 64 patients, 41 of whom (or 64 per cent) had normal records. Two of those who had abnormal records were excluded because the abnormalities of 1 could be attributed to administration of digitalis and those of the other to rheumatic heart disease. Twenty-one (or 33 per cent) of this group had abnormal electrocardiograms for which no cause other than hyperthyroidism was apparent.

The age group from 41 to 75 years consisted of 104 patients, 38 of whom (or 36.5 per cent) had normal records. Twenty-six of the group with abnormal records were excluded because of other etiologic factors. The abnormalities of the records of the remaining 40 patients (or 38.4 per cent) apparently were due only to hyperthyroidism. The increased proportion of abnormal records for the older age group may be attributed in part to degenerative heart disease which was not demonstrable by means other than the electrocardiogram. However, the electrocardiograms of 7 of 17 patients in this group reverted to normal after thyroidectomy.

The average basal metabolic rate was only slightly higher in the patients with abnormal electrocardiograms (45 per cent plus) than in those with normal records (37 per cent plus). In the younger age group the basal metabolic rate was the same for those with normal and those with abnormal records (42 per cent plus). In 8 patients with clinical hyperthyroidism (in 3 of whom the condition was recurrent) the basal metabolic rate was less than 15 per cent plus. For 5 other patients the basal metabolic rate had not been determined at the approximate time of the electrocardiographic studies. Exclusion of these two groups would not have altered the general findings in any way. They were included because the diagnosis in each instance had been well established clinically.

The approximate duration of symptoms of hyperthyroidism was only slightly longer for

the patients with abnormal electrocardiograms (twenty-six months) than for those with normal records (twenty months). This fact may be due in part to the greater number of older patients with abnormal electrocardiograms, the average duration of whose symptoms was thirty months, while the average duration of symptoms of those with normal records was only fifteen months. On the other hand, for the younger age group the average duration of symptoms of those with abnormal electrocardiograms was eighteen months and of those with normal records twenty-four months.

Although this series is not large, it is of interest to note that abnormalities were more common in the electrocardiograms of men than in those of women. Of 30 male patients, 21 (or 70 per cent) had abnormal records.

The average heart rate was approximately the same in all groups (100 per minute). Thus, tachycardia in hyperthyroidism in itself cannot account for the abnormalities, although it may bring out latent abnormalities in the records of the older age group in a manner similar to exercise.<sup>6</sup>

Sinus tachycardia (rate 100 or more) was the most common rhythm found in hyperthyroidism. It was present in 61 (or 43.5 per cent) of 140 patients at the time the electrocardiograms were taken. A significant degree of sinus arrhythmia was noted in only 4 patients. Ventricular ectopic beats were encountered in only 6 patients and auricular ectopic beats in only 1.

Auricular fibrillation was observed in 20 (or 14 per cent) of the 140 patients. Since this was a selected series, the incidence may have been somewhat higher than it would have been in a consecutive series. However, a survey of the literature showed that from 13 to 20 per cent of patients with hyperthyroidism have auricular fibrillation.<sup>7</sup> Baker, Bohning and Wilson.<sup>8</sup>

6 Twiss, A, and Sokolow, M. Angina Pectoris Significant Electrocardiographic Changes Following Exercise, *Am Heart J* **23** 498, 1942.

7 (a) Coelho, E. Les troubles cardiaques dans la maladie de Basedow et le myxoedeme. Etude electrocardiographique, *Ann de med* **30** 272, 1931. (b) Dancs-Shek, W. The Heart in Hyperthyroidism, Boston M & S J **190** 487, 1924. (c) Don, C S D, and Langley, G J. Some Aspects of the Electrocardiogram in Toxic Goiter, *Quart J Med* **1** 9, 1932. (d) Kammerer, H, and Obermaier, A. Elektrokardiographische Untersuchungen an Thyreotoxikosen vor und nach der Operation mit besonderer Berücksichtigung der T-Zacke, *Deutsches Arch f klin Med* **174** 117, 1932. (e) Rose, E, Wood, F C, and Margolies, A. The Heart in Thyroid Disease. II The Effect of Thyroidectomy on the Electrocardiogram, *J Clin Investigation* **14** 497, 1935. (f) White, P D, and Aub, J C. The Electrocardiogram in Thyroid Disease, *Arch Int Med*



noted that of their 108 hyperthyroid patients with auricular fibrillation 23 per cent had transient or paroxysmal auricular fibrillation. In our series auricular fibrillation was paroxysmal in 5 and chronic in 15 patients. In 5 of these the auricular fibrillation was converted to a sinus rhythm—in 2 after rest and treatment with iodine and in 3 after thyroidectomy. One patient, aged 59, who continued to have fibrillation three months after thyroidectomy, was given quinidine, with subsequent development of auricular flutter, which was later converted to a permanent auricular fibrillation. In another patient, aged 38, who had auricular fibrillation, bouts of auricular flutter had been demonstrated by electrocardiogram. Five weeks after thyroidectomy she again had a paroxysm of auricular flutter, but subsequent electrocardiograms have shown a normal sinus rhythm. For the remaining 12 patients with auricular fibrillation, no electrocardiograms were taken postoperatively, but 5 have had a normal rhythm clinically, 1 has had less frequent clinical paroxysms of auricular fibrillation, 3 have had persistent auricular fibrillation, 1 has died, and the status of 2 is not known. In the age group from 14 to 40 auricular fibrillation occurred infrequently (in 2 of 62 cases, or 3 per cent).

Diffuse toxic goiter occurred in 116 of the 140 patients, of these 12 had auricular fibrillation. Eight of the 24 patients with toxic nodular goiter had auricular fibrillation. Thus the incidence of auricular fibrillation was 10.3 per cent in diffuse toxic goiter and 33.3 per cent in toxic nodular goiter. When the younger age group, in whom auricular fibrillation occurred infrequently, was excluded, a different picture was presented. Of 46 patients with toxic diffuse goiter in the older age group, 10 (or 22 per cent) had auricular fibrillation. In the same age group, 8 (or 25 per cent) of the 32 patients with toxic nodular goiter had auricular fibrillation.

The average duration of symptoms of the patients with diffuse toxic goiter was approximately twenty months, and that of the patients with toxic nodular goiter was twenty-eight months. Among the 20 patients with auricular fibrillation the average duration of symptoms of

those with diffuse toxic goiter was twenty-nine months and of those with toxic nodular goiter seventy-three months. The striking difference in duration of symptoms, even for so small a series, suggested that the increased incidence of auricular fibrillation in cases of nodular goiter was associated with longer duration and with older age. The basal metabolic rates of the patients with the two types of goiter were approximately the same (44 per cent plus for patients with a diffuse toxic goiter and 46 per cent plus for those with toxic nodular goiter).

Partial auriculoventricular block or prolongation of the PR interval for age and heart rate<sup>9</sup> was found in 7 patients who had received no digitalis and in 2 patients who had been digitalized. The PR intervals of these 7 patients were

PR Interval	Rate	Age	Basal Metabolic Rate
0.19	105	16	44%+
0.19	107	25	45%+
0.20	113	27	53%+
0.24, 0.28	107	29	65%+
0.21	115	41	31%+
0.20	100	51	44%+
0.20	103	66	50%+

Three of these patients have had postoperative electrocardiograms, and the other 4 have had no further electrocardiograms.

Impairment of auriculoventricular conduction in hyperthyroidism has been recognized since de Vries Reilingh<sup>9</sup> in 1915 reported complete heart block, demonstrated by polygraph, in a 48 year old woman with hyperthyroidism and the Stokes-Adams syndrome. Prolongation of the PR interval was described in 1918 by Krumbhaar<sup>10</sup> as occurring in 2 of 51 patients with goiter (not all of whom had toxic goiter). Stein<sup>11</sup> in 1921 reported prolonged PR intervals for some patients. Kerr and Hensel<sup>7b</sup> reported a PR interval of 5/25 second in 3 of 181 cases of goiter (not all instances of toxic goiter). Willius, Boothby and Wilson<sup>7a</sup> observed 1 patient with a PR interval of 0.28 second (not influenced by atropine) in their series of 377 hyperthyroid patients. They believed that this condition was a contraindication to digitalis therapy. In a case of our series in which the PR interval had progressed from 0.24 to 0.28 second, the interval subsequently decreased to 0.24 second although digitalis had been administered preoperatively (fig 1). Dameshek<sup>8</sup>

22 766 (Dec.) 1918 (g) Willius, F. A., Boothby, W. M., and Wilson, L. B. The Heart in Exophthalmic Goiter and Adenoma with Hyperthyroidism, *M. Clin. North America* 7 189, 1923 (h) Kerr, W. J., and Hensel, G. C. Observations on the Cardiovascular System in Thyroid Disease, *California State J. Med.* 20:306, 1922, *Arch. Int. Med.* 31 398 (March) 1923.

8 Barker, P. S., Bohning, A. L., and Wilson, F. N. Auricular Fibrillation in Graves' Disease, *Am. Heart J.* 8 121, 1932.

9 de Vries Reilingh, D. Een zeldzame stoornis in de hartwerkzaamheid bij morbus Basedow, *Nederl. tijdschr. v. geneesk.* 11 1425, 1915.

10 Krumbhaar, E. B. Electrocardiographic Observations in Toxic Goitre, *Am. J. M. Sc.* 155 175, 1918.

11 Stein, G. C. W. On Electrocardiograms in Thyrotoxic Conditions, *Minnesota Med.* 4 82, 1921.



noted that of his 141 patients, 5, whose basal metabolic rates were 60 per cent plus or more, showed some degree of auriculoventricular block, but he had not excluded contributing factors. All but 1 of Dameshek's patients were under 37 years of age. The 7 patients of our series had an average basal metabolic rate of 47 per cent plus, or approximately the same as that of the patients with other electrocardiographic abnormalities. Goodall and Rogers<sup>12</sup> reported PR intervals of 0.3 second in cases of hyperthyroidism. On the other hand, Smith and Colvin<sup>13</sup> observed no PR interval of more than 0.17 second in their series of 120 cases. Rose, Wood and Margolies<sup>7e</sup> found no prolongation of the PR interval in their 106 patients with goiter except in 1 whose goiter was considered nontoxic (PR interval, 0.24 second).

these (or 28 per cent) there was notching. The P wave was abnormally wide in lead I or II in 7 cases (or 5 per cent). In 3 cases the wide P waves were also notched, and in 1 case they were abnormally high. One other instance of an abnormally high P wave in lead II was seen. Diphasic P waves in lead I or II were encountered in only 1 case. Our observations do not corroborate previous reports in which high P waves were regarded as characteristic of hyperthyroidism.

Many observers have considered the amplitude of the QRS complex in hyperthyroidism to be high. None of the patients in our series had QRS amplitudes above the recognized limits of normal (35 mm).<sup>4</sup> Of 32 patients who had electrocardiograms taken after thyroidectomy, 6 had lowered QRS voltage (3 of these had proved

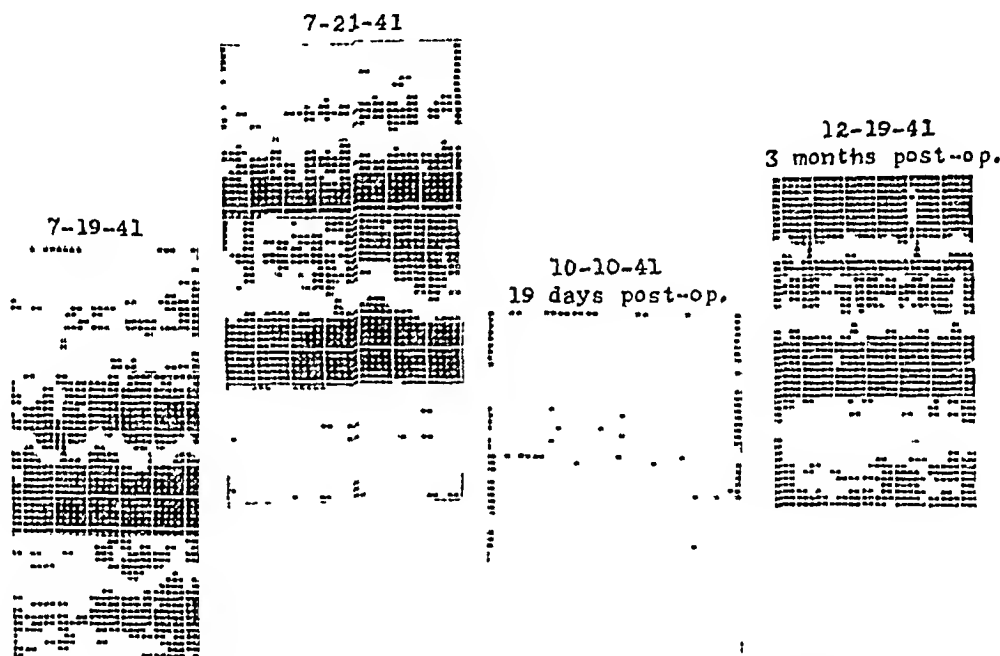


Fig 1—Tracings of a woman aged 29 with diffuse toxic goiter of two months' duration (basal metabolic rate 65 per cent plus). Partial auriculoventricular block and a flat  $T_1$  were becoming normal after thyroidectomy.

No case of complete auriculoventricular block was observed in our series. It is noteworthy that in the reported cases of hyperthyroidism associated with complete heart block there has been complicating acute infection or digitalization.<sup>14</sup>

Variations in the P wave were observed in 44 (or 31 per cent) of the 140 cases. In 39 of

12 Goodall, J. S., and Rogers, L. The Electrical and Histological Manifestations of Thyrotoxic Myocarditis, *Brit M J* 1:1141, 1927.

13 Smith, F. J., and Colvin, L. T. Certain Cardiovascular Features of Hyperthyroidism, *Ann Clin Med* 5:616, 1927.

14 Cameron, J. D. S., and Hill, I. G. W. Heart Block in Toxic Goiter. A Report of Two Cases, *Edinburgh M J* 39:37, 1932. Davis, A. C., and Smith, H. L. Complete Heart-Block in Hyperthyroidism Following Acute Infections. A Report of Six Cases with Necropsy Findings in One Case, *Am Heart J* 9:81, 1933.

myxedema). The duration of the QRS complex was prolonged in 5 cases, in 2 of these the duration was 0.11 second, in 2 right bundle branch block occurred and in 1 there was left bundle branch block. The ages of the patients were 57, 57, 51, 42 and 33 years, thus 4 were in the older age group. We believe that the prolonged QRS complex in these cases probably was due to coexisting disease of the coronary artery rather than to hyperthyroidism. One patient in our series had a prolonged QRS complex with a short PR interval, the so-called bundle of Kent, associated with paroxysmal auricular fibrillation. After thyroidectomy, repeated electrocardiograms have been normal, although less frequent paroxysms of auricular fibrillation have been noted clinically.

Abnormal deviation of the axis to the left was encountered in tracings of 7 patients of the older

group. In no case was it altered significantly after thyroidectomy. Deviation of the axis to the right occurred in the tracings of 2 young patients, in both of whose cases it was referable to body build. In 3 cases the electrical axis shifted toward the right after thyroidectomy, but it did not vary significantly in any other case.

In many of the records slight elevation or depression of the ST segment was seen, but it was always within normal limits except in cases in which digitalis had been given or in which hypertension was present.

In the past, high T waves have been considered characteristic of hyperthyroidism.<sup>15</sup> White and Aub,<sup>16</sup> in 1918 were among the first to cast doubt on this concept. They stated "In hyperthyroidism, the T wave is often low and its height does not parallel necessarily

not characteristic of our series. In the tracing of only 1 patient (who also had hypertension) the T waves in leads I and II exceeded the upper limits of normal (6 mm)<sup>5</sup>; they measured 6 mm in lead I and 8 mm in lead II. In the normal records the highest T<sub>1</sub> was 4 mm and the average was 2.3 mm (the average standard of Ashman and Hull<sup>3</sup> is 2 mm). The highest T<sub>2</sub> in the same records was 5.5 mm, and the average was 3.1 mm (average standard, 3 mm). Measurements of the T wave were omitted in the cases of 19 of the 61 patients with abnormal records because of coexisting prolongation of the QRS complex, hypertension or administration of digitalis. T<sub>1</sub> was abnormal in 23 and T<sub>2</sub> in 22 of the remaining 42 cases. Thus, of 121 cases in which the T waves apparently were not influenced by other factors, T<sub>1</sub> was abnormal



Fig 2—Tracings of a man aged 55 with diffuse toxic goiter of one hundred and twenty months' duration (basal metabolic rate 29 plus). T<sub>1</sub> was low and T<sub>2</sub> of unusual contour. Paroxysmal auricular fibrillation was noted two days after thyroidectomy. The patient was normal two months after operation and had myxedema with low QRS and T waves three years postoperatively.

changes in the height of the metabolism, it sometimes runs conversely to it." Krumbhaar<sup>10</sup> noted that the T waves in leads I and II occasionally were diphasic and inverted and thought this signified a poor prognosis. Kerr and Hensel<sup>7b</sup> observed that T<sub>1</sub> or T<sub>2</sub> was low in the tracings of 6 patients who had advanced myocardial disease, 2 of whom died. Low or inverted T waves have subsequently been observed in association with hyperthyroidism by many authors.<sup>16</sup> Abnormally high T waves were

in 19 per cent and T<sub>2</sub> in 18 per cent. Abnormalities of T waves in both leads I and II in the same record occurred in 12 cases, or 10 per cent. Low amplitude was the most common abnormality (25 instances). Abnormalities were notching in 12, diphasic T waves in 9

<sup>15</sup> Hoffmann, A. Die Elektrographie als Untersuchungsmethode des Herzens und ihre Ergebnisse, Wiesbaden, J. F. Bergmann, 1914, p. 108, cited by Coelho,<sup>7a</sup> cited by Stein.<sup>11</sup>

<sup>16</sup> Katz,<sup>5</sup> Coelho,<sup>7a</sup> Don and Langley,<sup>7c</sup> Kammerer and Obermaier,<sup>7d</sup> Rose, Wood and Margolies,<sup>7e</sup> Willius,

Boothby and Wilson,<sup>7f</sup> Goodall and Rogers,<sup>12</sup> Smith and Colvin,<sup>13</sup> Hamburger, W. W., Leo, M. W., Priest, W. S., and Howard, H. D. The Heart in Thyroid Disease. I. Changes in the T Wave of the Human Electrocardiogram Following Iodine Medication and Thyroidectomy, Arch. Int. Med. **43**: 35 (Jan.) 1929. Graybiel, A., and White, P. D. Inversion of the T-Wave in Lead I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia with Thyrotoxicosis in Relation to Certain Infections and Following Paroxysmal Ventricular Tachycardia, Am. Heart J. **10**: 345, 1935.

and abnormal contour in 4 cases. These abnormalities occurred about as frequently in the cases of younger patients (in 22 cases) as in those of the older age group (in 23 cases). Although a characteristic "rolling" contour of the "thyroid T wave" has been described by McGuire and Foulger,<sup>17</sup> we are unable to recognize any typical contour of the T wave in our series.

Studies to determine the causes of the abnormalities in the T waves will be discussed in a later paper; hyperventilation was found to be one factor.

Follow-up studies after a period of rest and administration of iodine or after thyroidectomy

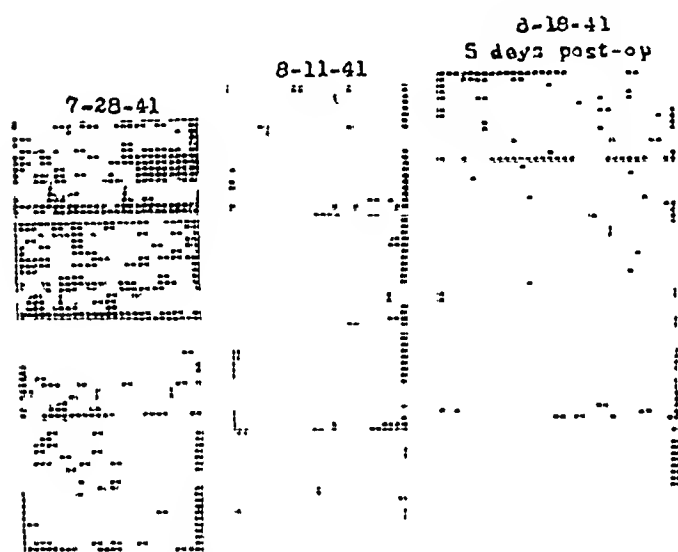


Fig 3—Tracings of a woman aged 22 with diffuse toxic goiter of twelve months' duration (basal metabolic rate 41 per cent plus). Low notched  $T_1$  and  $T_2$  and diphasic  $T_4$  were nearly normal two weeks after rest and treatment with iodine, and the tracing was normal after thyroidectomy.

were made in 17 cases in which the T waves had been abnormal. In 14 of these the preexisting abnormalities had disappeared, in 7 the only abnormal T wave was in lead I, in 4 the abnormal T wave was in lead II, and in 4 the T waves in both leads I and II were abnormal. In 3 cases the abnormalities persisted,  $T_1$  in 1 case,  $T_2$  in the second case and both  $T_1$  and  $T_2$  in the third case.

#### SUMMARY

Among 168 patients for whom electrocardiograms were taken during the period of thyro-

toxicosis, 140 showed no causes other than hyperthyroidism for any possible electrocardiographic abnormalities. Of the 168 patients, 79 (or 47 per cent) had normal records, while 89 (or 53 per cent) had abnormal ones. Sixty-two of the 140 patients were in the age group from 14 to 40 years and 78 in the age group from 41 to 75 years. Seventy-three per cent had diffuse toxic goiters, and 27 per cent had toxic nodular goiters. Seventy-nine per cent were women, and 21 per cent were men. Electrocardiograms demonstrated auricular fibrillation in 14 per cent of the cases. Prolongation of the PR interval for age and heart rate occurred in 5 per cent. Of 121 patients without other causes for abnormalities in the T waves, 19 per cent had abnormalities of  $T_1$ , 18 per cent of  $T_2$  and 10 per cent of  $T_1$  and  $T_2$  in the same record. Auricular fibrillation was the only abnormality the incidence of which was not fairly equal for the younger and the older age group.

Electrocardiograms taken after treatment of hyperthyroidism showed disappearance of abnormalities of the T waves of 14 of 17 patients, with persistence of the abnormalities in 3 patients. Auricular fibrillation was replaced by a normal rhythm in 7 of 8 patients reexamined and persisted in 1. Of the patients with partial auriculoventricular block, 3 had postoperative electrocardiograms which showed the auriculoventricular conduction time to be normal.

#### CONCLUSIONS

In our series of cases of hyperthyroidism the noteworthy electrocardiographic findings in order of frequency were (1) sinus tachycardia, (2) various abnormalities of the T waves, of which low amplitude and notching were the most common, (3) auricular fibrillation, (4) partial auriculoventricular block, and (5) in rare instances auricular flutter. After exclusion of other causes for electrocardiographic abnormalities, the incidence of these findings was the same for the younger (14 to 40 years) and for the older (41 to 75 years) group of patients. After treatment of hyperthyroidism, the abnormalities tend to disappear. In the presence of hyperthyroidism, electrocardiograms must be interpreted with caution, since they may simulate those of persons with organic heart disease.

Miss Jean Hitch, secretary of the Thyroid Clinic, and Miss Ola Nagle, of the Electrocardiographic Laboratory, assisted in compiling data.

17 McGuire, J, and Foulger, M. The Influence of Thyroid Extract and Hyperthyroidism on the Electrocardiogram, with Special Reference to the T-Waves. *Am Heart J* 8:114, 1932.

# Progress in Internal Medicine

## GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM  
JULY 1942 TO JULY 1943

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(Continued from page 108)

### CLINICAL ASPECTS (CONTINUED)

*Intestinal Obstruction*—The detailed physiology of intestinal ileus continues to receive attention, and a study by Oppenheimer and Mann<sup>263</sup> was undertaken to determine the role of intestinal capillary circulation during varying degrees of intraluminal pressure, with particular regard to intestinal viability. Definite capillary patterns were seen in experimental obstruction, and it appeared that intraparietal capillary flow ceases when the intraluminal pressure reaches a level of about 60 mm of mercury. Lower pressures produce little or no change in the intraparietal capillary circulation. Reactive hyperemia followed deflation in all the experiments, and it was noted that angulation or twisting of extramural vessels resulted in cessation of capillary flow at the lower values of distending pressure (less than 30 mm).

Evans<sup>264</sup> presents studies on shock in intestinal strangulation, with particular observations on loss of plasma. He emphasizes the earlier studies of Blalock, who pointed out the importance of an intelligent appraisal of the various causes of shock, which must include differentiation between the initiating factor and the sustaining or terminal factor. Evans groups under three general headings the factors he believes to be important in the causation of shock in intestinal strangulation. The initial phase is associated with obstruction of venous flow but not with impairment of arterial flow, with resulting increased capillary filtration locally and loss of plasma. The second is a sustaining phase, in which the plasma pressure remains elevated as long as the loss of plasma can be compensated for by a protective vasomotor mechanism. In this phase only local damage results until excessive loss of plasma causes a fall in blood pressure and a diminution in cardiac output and a generalized increase in capillary permeability. The terminal phase is one of generalized damage to the capillaries, with further leakage of protein and fluid from the vascular bed, pulmonary edema and eventually necrosis of the intestinal mucosa, with permeability to the contents of the obstructive loop.

A study by Abbott and his associates<sup>265</sup> was undertaken to evaluate quantitatively the changes in plasma volume and in the "available fluid" (extracellular) in experimental obstruction at various levels of the intestinal tract. The conclusions are well presented, although not new, and with the preceding paper clarify the therapeutic indications in cases of intestinal obstruction. The amount of gastro-

263 Oppenheimer, M. J., and Mann, F. C. Intestinal Capillary Circulation During Distention, *Surgery* **13** 548, 1943.

264 Evans, E. I. The Mechanism of Shock in Intestinal Strangulation. An Experimental Study, *Ann Surg* **117** 28, 1943.

265 Abbott, W. E., Mellors, R. C., and Muntwyler, E. Fluid, Protein and Electrolyte Alterations in Experimental Intestinal Obstruction, *Ann Surg* **117** 39, 1943.

intestinal fluid lost varies greatly, depending on the level and degree of obstruction and the amount and frequency of vomiting. A deficit of body water, usually resulting from a diminished intake and an excessive loss, may be greatly accelerated when distention, strangulation, hemorrhage or infection occurs. The rapidity of loss of body water depends on the number of causes present and the severity of each. The hematocrit reading and the protein and the chloride content of the plasma cannot be employed to estimate quantitatively the decrease in plasma volume. A deficit in the total circulating plasma protein may be considerable in cases of prolonged intestinal obstruction, and this loss is frequently masked by hemoconcentration. Successful treatment depends largely on the completeness with which body water can be restored and on the prevention of further loss.

Motility of the small bowel was found by Leigh<sup>266</sup> to be markedly depressed in cases of ileus associated with edema of the bowel. Deflation can best be treated by measures directed toward raising the plasma protein concentration and thereby modifying the constitutional state of the patient. He emphasizes a point which is still not adequately recognized—that therapy directed to replacement of fluid and salt will increase the edema as long as the plasma protein concentration remains at edema level. He might well have added that such replacement therapy can in part be avoided by the intelligent use of salt-free fluids until normal plasma protein relationships are restored.

As a rule, the diagnosis of intestinal ileus can be confirmed by careful roentgen studies. Stadler<sup>267</sup> cites 2 cases in which incomplete intestinal obstruction was associated with typical clinical symptoms but results of roentgen studies carefully carried out were absolutely noncontributory. Goldman<sup>268</sup> comments on the same phenomenon and presents a case history and animal experiments in substantiation. In 10 animals sudden production of strangulating obstruction of a loop of small bowel produced typical roentgenologic evidence, but in 75 per cent of 20 other dogs, in which the strangulating obstruction was produced by gradual interference with the blood supply and later with the wall of the bowel itself, roentgenograms failed to show typical changes. Such observations obviously imply the necessity for careful examination and evaluation of the clinical picture as the most important measures in dealing with this condition.

Levitin and Trauner<sup>269</sup> also discuss the postoperative roentgenologic findings in the abdomen and state that postoperative distention is usually in the nature of paralytic ileus, which is independent of the type of anesthesia used. Mechanical block may exist without clinical manifestations. When demonstrated and treated surgically, the bowel returns to normal almost immediately, as viewed in the roentgenogram. A positive roentgenographic diagnosis of mechanical obstruction is definite, regardless of the presence or absence of clinical symptoms. Like the preceding authors, they note that negative roentgen findings in a clinically distended abdomen do not rule out the presence of severe abdominal pathologic change.

Unusual causes for intestinal obstruction may be mentioned briefly. Fagarasanu<sup>270</sup> cites an instance of duodenal occlusion due to an internal hernia in the

266 Leigh, O. C., Jr. Ileus Associated with Edema of the Bowel, *Surg., Gynec. & Obst.* **75** 279, 1942.

267 Stadler, H. E. The Preeminent Importance of Clinical Signs in the Diagnosis of Intestinal Obstruction in Early Infancy, *J. A. M. A.* **120**:1384 (Dec. 26) 1942.

268 Goldman, L. Intestinal Strangulating Obstruction with Negative Roentgenologic Findings, *Surgery* **13** 834, 1943.

269 Levitin, J., and Trauner, L. M. A Roentgenological Study of the Postoperative Abdomen, *Surg., Gynec. & Obst.* **75** 510, 1942.

270 Fagarasanu, I. Rare Cause of Duodenal Occlusion. Internal Retroduodenal Hernia, *Wien. med. Wchnschr.* **91** 857, 1941.

retroduodenopancreatic recesses Palmer<sup>271</sup> notes what must be an unusual clinical manifestation, namely, recurrent attacks of subacute intestinal obstruction due to extreme tortuosity of the abdominal aorta, which caused pressure on the left portion of the transverse colon Approximately 7 cases of primary calculi of the small bowel causing obstruction have been reported in the literature DeWitt and his associates<sup>272</sup> describe such a condition in a man of 26, who complained of sudden onset of abdominal cramps and vomiting The cause of the obstruction, which was localized in the proximal portion of the ileum, was a huge fecolith composed largely of vegetable fibers

Obstruction due to gallstones is common, but certain points of clinical interest may be mentioned in commenting on reports by Hinchey,<sup>273</sup> Hand and Gilmore<sup>274</sup> and Hodson<sup>275</sup> Over 200 cases have been reported to date, and according to the literature instances of obstruction due to biliary calculi constitute about 1 to 2 per cent of all cases In the majority of cases the terminal part of the ileum is the site of obstruction Hinchey mentions 6 patients in whom gallstones were localized in the jejunum The operative mortality is high—50 per cent in some reports For this reason it is wise to postpone surgical intervention in the absence of definite obstruction until roentgen examination makes it apparent that the progress of the discovered stones has stopped One of Hinchey's cases apparently involved a stone which had been observed in the small bowel over a period of five years without obstructive symptoms Immediate exploration in the face of obstruction is obviously indicated A point made by Hand and Gilmore is of some interest, namely, that when a large facet is noted on a gallstone removed from the bowel one should account for the second stone to avoid a possible recurrence of ileus A rather unusual case is that reported by Hodson, of a woman of 80 years, in whom roentgen examination indicated two stones in the gallbladder and two in the region of the lower part of the ileum Operation for obstruction was performed, and one of the ileal stones causing obstruction was located and successfully removed The other could not be located but subsequently was passed, as shown by roentgen studies

Intussusception is essentially a disease of infancy and early childhood A report by Rowe<sup>276</sup> of 10 cases of its occurrence in adults, therefore, is of some interest Eight of the patients presented the usual clinical picture of chronic recurrent intussusception, due to varying causes Such a condition does not involve emergency surgical intervention, but operation should not be unduly delayed once the diagnosis has been established Two other patients with intussusception were included The underlying causes were the usual ones, such as tumor of the small bowel, Meckel's diverticulum, mesenteric glands and previous operation Primary intussusception usually starts in the ileocecal angle For this reason a more exact definition of "mobile cecum" is of importance, because of the association of this condition with acute intussusception or volvulus Ingelfinger<sup>277</sup> presents careful

271 Palmer, R S A Case of Marked Tortuosity of the Abdominal Aorta Without Calcification, Causing Mild Attacks of Subacute Intestinal Obstruction, *Ann Int Med* **17** 358, 1942

272 DeWitt, W F, Morrissey, P G, Jr, and Failla, S D Obstruction of the Small Intestine from a Primary Calculus, *Mil Surgeon* **92** 34, 1943

273 Hinchey, P R Gallstone Ileus, *Arch Surg* **46** 9 (Jan) 1943

274 Hand, B H, and Gilmore, W E Gallstone Ileus, *Am J Surg* **59** 72, 1943

275 Hodson, C J A Case of Intestinal Obstruction Due to Gallstones, *Brit J Radiol* **16** 185, 1943

276 Rowe, P G Intussusception in Adults, *Canad M A J* **47** 219, 1942

277 Ingelfinger, F J Intermittent Volvulus of the Mobile Cecum, *Arch Surg* **45** 156 (July) 1942

studies on intermittent volvulus of the mobile cecum. In order to give the term real clinical significance, he limits the expression "mobile cecum" to a cecocolon which usually lies in its proper position but which potentially is subject to a process of rotation in the intact abdomen of the living person. Acute cecal volvulus is relatively infrequent. Somewhat under half of the patients with acute cecal volvulus have suffered from chronic symptoms before the acute attack. Ingelfinger presents roentgenograms in a typical case, demonstrating that the cecocolon could rotate easily through an angle of 180 degrees and that transient intestinal obstruction could occur. He discusses the diagnostic value of Miller-Abbott intubation in this condition.

A more unusual example of intestinal volvulus is described by River and Gubler<sup>278</sup> in which the volvulus was localized and the megacolon limited to the transverse portion of the large bowel. The lesion was demonstrated adequately by roentgen examination. Volvulus of the sigmoid is an occasional cause of obstructive ileus. It is rare in young people, and the most important etiologic factor is a long mesentery with a narrow attachment to the posterior abdominal wall. Excellent illustrations of the condition are given by Hinton and Steiner<sup>279</sup> and Metheny and Nichols<sup>280</sup>. The latter describe the extremes in age incidence, 1 patient being 3 months old and another 93 years.

The details of the successful management of intestinal obstruction have been fully emphasized in many articles during recent years, and the principles underlying such therapy are being more generally emphasized by careful attention to replacement therapy, decompression and recognition of the physiologic disturbances occurring in shock. The result of the applications of these principles is apparent in the improvement in mortality statistics, as shown, for example, in an article by Smith and van Beuren<sup>281</sup>. These authors report a study of the cases of 580 patients with acute ileus treated over a period of twenty-four years. The cases are divided into six periods of four years. During the first twenty years, mortality was gradually reduced from 66.6 per cent to 28.4 per cent by the application of improved general surgical methods. In the last period, after the use of the Miller-Abbott tube, the mortality was still further reduced, to a level of 23.8 per cent. An important fact emerges from their statistics, namely, that in patients operated on after forty-eight hours no real improvement in operative results has been obtained in the last twenty years. They comment on the value of intra-abdominal use of sulfanilamide powder, but correctly state that it is not a good substitute for proper surgical intervention. Even lower mortality figures are reported in comparable groups treated during the same four year period by Noer and Johnston<sup>282</sup> and Dennis and Brown<sup>283</sup>. These authors record postoperative mortality since the use of decompression methods of 19.9 per cent and 17.9 per cent, respectively. In spite of a general improvement in the results of treatment of acute intestinal obstruction, a

278 River, L. P., and Gubler, J. A. Transverse Megacolon Associated with Chronic Volvulus, *Ann Surg* **117** 786, 1943.

279 Hinton, D., and Steiner, C. A. Recurrent Volvulus of the Sigmoid Colon. An Unusual Case Report, *Ann Surg* **116** 147, 1942.

280 Metheny, D., and Nichols, H. E. Volvulus of the Sigmoid, *Surg, Gynec & Obst* **76** 239, 1943.

281 Smith, B. C., and van Beuren, F. T. Acute Ileus. Analysis of One Hundred and Thirty Operated upon at the Presbyterian Hospital, New York City from 1936-1939 Inclusive, with Use of the Miller-Abbott Tube in 1938 and 1939, *Ann Surg* **117** 427, 1943.

282 Noer, R. J., and Johnston, C. G. Small Intestine Obstruction, *Ann Surg* **115** 935, 1942.

283 Dennis, C., and Brown, S. P. Treatment of Small Bowel Obstruction. Procedure Used at the University of Minnesota Hospitals, *Surgery* **13** 94, 1943.



persistent mortality, varying from 12 to 20 per cent, is still reported. Wangenstein<sup>284</sup> makes the pertinent statement that in these figures a definite mortality of treatment should be identified. Too enthusiastic reliance on suction management, as he points out, contributes to the mortality of treatment, owing largely to the uncompensated loss of fluid and electrolytes and to overoptimism resulting from palliation of symptoms.

Any method which aids in determining the viability of the bowel is of great importance in the surgical management of intestinal strangulation. For this reason, a preliminary report of Herrlin and his associates<sup>285</sup> is of interest. They describe the use of fluorescein, whereby direct visual evidence concerning the viability of the injured portion of the intestine can be established immediately. They also mention the diagnostic and therapeutic help that may be obtained by the injection of procaine hydrochloride along the vessels leading to a strangulated loop, with resulting release of vascular and muscular spasm.

*Appendicitis*—Although there is an increasing awareness of the problem of appendicitis by the laity, it is pertinent to point out to physicians diagnostic difficulties arising in relation to this condition. For this reason brief mention will be made of various recent articles bearing on the diagnosis of appendicitis and its complications. A careful analysis of 100 cases of acute gastroenteritis and 60 cases of acute appendicitis in university undergraduates is presented by Quigley and Contratto<sup>286</sup>. In many instances a differential diagnosis was extremely difficult. Characteristic of acute gastroenteritis were explosive onset of colicky pain, which was usually poorly localized, vomiting, diarrhea, high fever and a white blood count of less than 10,000, with bizarre or no abdominal signs. In the cases of appendicitis, almost invariably the onset was insidious, with steady abdominal pain. Tenderness and true spasm were diagnostic signs of the greatest importance, and rebound or cough tenderness referred to the right lower quadrant of the abdomen was almost pathognomonic.

The association of appendicitis with common contagious diseases was studied by Goodman and Silverman<sup>287</sup>. Among nearly 30,000 cases of common contagious diseases were found 153 cases of acute appendicitis proved by gross and microscopic evidence. The greatest incidence was noted in patients with measles and with varicella. Of particular importance is the fact that in more than one half of 102 cases of acute appendicitis occurring in association with contagious diseases the appendix was found to be ruptured at operation. Such a finding indicates that the possibility of acute appendicitis as a concomitant of the exanthematous or other contagious diseases is frequently overlooked and necessary operation thereby delayed.

A source of diagnostic difficulty that is fortunately rather uncommon in this country is the confusion caused by the occasional association of acute appendicitis with typhoid. This is especially true in the prodromal stages of typhoid when a clearcut diagnosis is not obvious and when symptoms point to the lower right

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284 Wangenstein, O. H. *New Operative Techniques in the Management of Bowel Obstruction, Surg., Gynec. & Obst.* **75**: 675, 1942.

285 Herrlin, J. O., Jr., Glasser, S. T., and Lange, K. *New Methods for Determining the Viability of Bowel. Preliminary Report with Clinical Cases, Arch. Surg.* **45**: 785 (Nov.) 1942.

286 Quigley, T. B., and Contratto, A. W. *Differential Diagnosis of Acute Appendicitis and Acute Gastroenteritis in College Men, New England J. Med.* **226**: 787, 1942.

287 Goodman, M., and Silverman, I. *Acute Appendicitis in Patients with the Common Contagious Diseases, New England J. Med.* **228**: 533, 1943.

quadrant of the abdomen. For this reason the article by Inda and his associates<sup>288</sup> is worthy of comment. Although mentioned in previous literature, the simulation of acute appendicitis by acute strain of the rectus muscle is not fully appreciated. Eight cases are reported by Bowers and Richard.<sup>289</sup> In only 1 was a correct diagnosis made prior to the patient's admission to the station hospital. Other conditions rarely simulating acute appendicitis are infectious mononucleosis<sup>290</sup> and the bite of the black widow spider.<sup>291</sup>

A physical sign that conceivably may be of diagnostic importance is one reported by Capurro,<sup>292</sup> who attributes it to hyperesthesia of the posterior portion of the peritoneum. Deep palpation of the region of the iliac muscle, which is internal to and above the crest of the anterior iliac spine, provokes pain that is localized, according to this author. The reaction is apparently independent of the position of the appendix and applies to patients with little or no abdominal spasticity. Another diagnostic point of some consequence is stressed by Stevens,<sup>293</sup> who comments on the value of auscultation of the abdomen in the diagnosis of acute appendicitis. He claims that he has never seen a patient with acute appendicitis at or near the time of rupture who had a noisy abdomen. He cites various exceptions, and it is obvious that this is merely one other physical sign of importance, rather than pathognomonic evidence.

Appendicitis in its protean manifestations frequently interests the gynecologists. Damage to the right adnexal structures through inflammation primary in the appendix is well known. Less frequently reported is left-sided abdominal and pelvic infection during or subsequent to inflammation of the appendix. Three instances of such a complication are recorded by Faulkner and Weir.<sup>294</sup> Another unusual complication is the occurrence of an umbilical discharge secondary to appendicitis. This may occur as a consequence of spontaneous rupture of an appendiceal abscess resulting in an enteroumbilical fistula, or it may be caused by a generalized peritonitis secondary to inflammation of the appendix. Illustrative cases of such complications are described by Allen and Johnson.<sup>295</sup>

The presence of fecoliths is known to be an important factor in the production of acute attacks. The diagnosis of such appendiceal fecoliths is occasionally made and may warrant surgical intervention. Jackman<sup>296</sup> calls attention to the roentgenologic aspects. A rather odd finding, which concerns the retention of material in the appendix, is reported by Sanes and Ambrusko.<sup>297</sup> Out of a series of 1,395 appendices examined histologically, 17 specimens showed the presence of a peculiar

288 Inda, F. F., Natin, I., and Lefevre, H. The Appendix in Typhoid Fever, *Semana méd.* **2** 1512, 1941.

289 Bowers, W. F., and Richard, N. F. Rectus Muscle Strain Simulating Acute Appendicitis, *Mil. Surgeon* **92** 645, 1943.

290 Straus, R. Infectious Mononucleosis Simulating Acute Appendicitis, with Description of a Specific Lesion of the Appendix, *Am. J. Clin. Path.* **12** 295, 1942.

291 Wilson, H. Acute Abdominal Symptoms in Arachnidism. Black Widow Spider Bite, *Surgery* **13** 924, 1943.

292 Capurro, R. Hyperesthesia of the Posterior Peritoneum (Objective Pain) in Appendicitis and Other Visceral Lesions, *Ann. Surg.* **117** 735, 1943.

293 Stevens, N. C. The Value of Auscultation of the Abdomen in the Diagnosis of Acute Appendicitis, *Am. J. Surg.* **60** 365, 1943.

294 Faulkner, R. L., and Weir, W. C. Left-Sided Pelvic Lesions Subsequent to Appendicitis. Report of Three Cases, *Am. J. Obst. & Gynec.* **45** 874, 1943.

295 Allen, P. D., and Johnson, R. A. Umbilical Discharge in Acute Appendicitis, *Ann. Surg.* **117** 473, 1943.

296 Jackman, J. The Roentgen Diagnosis of Appendiceal Fecoliths, *Am. J. Roentgenol.* **48** 803, 1942.

297 Sanes, S., and Ambrusko, J. The Microscopic Diagnosis of Radiopaque Substance in the Vermiform Appendix, *Surgery* **13** 561, 1943.

substance at the lumen of the appendix, which was subsequently identified as barium sulfate. In 9 of the cases the appendix had been removed for interval or "chronic" appendicitis. The clinical implication of such a finding is discussed by the authors, who refer to Holmes's statement that "in the so-called chronic appendix where the infection has come and gone, there may be no evidence of the process other than fixation and failure to empty. An appendix which retains barium several days after the ascending colon has emptied is a potential source of trouble."

The mortality from appendicitis, although still an important figure, shows signs of gradual reduction, in all probability due to educational campaigns and the use of chemotherapy. Reports on large series of cases are presented by Watkins<sup>298</sup> and Dennis and his associates<sup>299</sup>. Nineteen thousand, four hundred and one cases encountered from 1930 to 1941 inclusive are reported by Watkins to have shown a decline in mortality from 6.8 per cent in 1930 to 2.8 per cent in 1941. Dennis records the results in 1,393 cases, with an over-all mortality of 1.75 per cent. He ventures the opinion, which should be taken seriously, that in spite of the fact that it requires the expenditure of more hospital days, drugs, blood and care conservative therapy is probably the treatment of choice in cases of appendicitis with spread of the disease beyond the appendix itself.

A highly informative and honest analysis of the problem of chronic appendicitis is to be found in the report of Willauer and O'Neil<sup>300</sup>. These authors made a study of 375 cases of patients who were operated on because of pain in the right lower quadrant of the abdomen. Microscopic examination of the surgical specimens revealed the fact that histologically there was no evidence of appendicitis in 104. Such a study is an obvious indication for the need of a really honest and careful examination of patients who present the symptoms of recurrent pain in the right lower quadrant, if unnecessary surgical operations are to be avoided.

A possible therapeutic measure for the treatment of peritoneal infection such as may occur as a sequel of appendicitis, is discussed by Miley and Rebbeck<sup>301</sup>. These authors attempt to control peritoneal infection and toxemia by means of ultraviolet irradiation of the blood. The material studied consists of 72 serial and unselected cases of peritonitis. In 29 chemotherapy had admittedly failed. In the remainder there had been no therapy for the control of the infection except the use of irradiated citrated blood. There was complete absence of reactions. Of the 72 patients so treated, 40 were said to have generalized peritonitis and 32 of these recovered. Such a therapeutic measure warrants critical consideration, if the accuracy of the diagnosis in the individual cases can be accepted.

Carcinoid tumors of the appendix may be benign, but there can be little doubt that they represent potentially malignant lesions. Insistence on the essentially malignant possibilities of such tumors is stressed by various authors, and several histologic variations of such tumors are described (Hopping, Dockerty and Masson<sup>302</sup>, Satory<sup>303</sup>, Uihlein and McDonald<sup>304</sup>, Young and Wyman<sup>305</sup>).

298 Watkins, R. M. Appendicitis in Cleveland, J. A. M. A. **120** 1026 (Nov 28) 1942

299 Dennis, C., Mears, F. B., and Ramsay, B. H. Treatment of Acute Appendicitis at the University of Minnesota Hospitals, Surg., Gynec. & Obst. **74** 1112, 1942

300 Willauer, G. J., and O'Neil, J. F. Late Postoperative Follow-Up Studies on Patients with Recurrent Appendicitis, Am. J. M. Sc. **205** 334, 1943

301 Miley, G. P., and Rebbeck, E. W. The Knott Technique of Ultraviolet Blood Irradiation as a Control of Infection in Peritonitis, Rev. Gastroenterol. **10** 1, 1943

302 Hopping, R. A., Dockerty, M. B., and Masson, J. C. Carcinoid Tumor of the Appendix. Report of a Case in Which Extensive Intra-Abdominal Metastasis Occurred Including Involvement of the Right Ovary, Arch. Surg. **45** 613 (Oct) 1942

A curious and rather rare condition involving the appendix is mucocele. One case of this lesion is reported by Lynch and Dixon,<sup>306</sup> in which the mucocele caused a tremendous dilatation of the appendix, which bulged into the cecum for 1½ to 2 inches (3.8 to 5 cm). The preoperative diagnosis, on the basis of roentgen examination, was a polypoid lesion of the cecum. Among other intra-abdominal conditions causing acute attacks that may simulate appendicitis, reference may be made to complications secondary to epiploic appendages. The surgical significance of these is discussed in articles by Giffin and his associates<sup>307</sup> and Harte.<sup>308</sup> Myers and Zollinger<sup>309</sup> call attention to one other possibility, namely, the occurrence of gastrointestinal symptoms in the presence of inguinal hernia. Such symptoms, if well established, may indicate basic or antecedent causes other than the proved hernia and should be evaluated before surgical intervention.

*Diverticulitis*—Diverticulosis may occur at any level of the gastrointestinal tract and is a common and usually asymptomatic condition. The roentgen diagnosis of duodenal diverticulosis was first described by Case in 1913, although the original description was given by Chomel in 1710. Since Case's report nearly 400 cases have been mentioned in the literature. A careful anatomic description of duodenal diverticula and variations of the duodenum is given by Ackermann,<sup>310</sup> based on studies of anatomical specimens. The probable incidence among adults, according to Finney,<sup>311</sup> is between 1 and 1.5 per cent. He wisely warns against intensive therapy except in an occasional case.

In 2 instances diverticula of the duodenojejunal flexure apparently caused serious diarrhea and were diagnosed for some time as "colitis." These cases are reported by Schoen.<sup>312</sup> Similar lesions in the jejunum, either single or multiple, also may be the source of symptoms requiring surgical intervention. Very few instances of such lesions associated with an acute inflammatory process or perforation have been recorded. Ovens<sup>313</sup> reports the occurrence of a diffuse generalized peritonitis secondary to jejunal diverticulitis, which was successfully treated by resection. The surgical risk from removal of jejunal diverticula obviously is distinctly lower than that associated with operation on the duodenum, and surgical removal of such lesions should therefore be approached with less hesitation, as pointed out by van Ravenswaay and Winn,<sup>314</sup> in the event that

303 Satory, J. J. Malignant Carcinoid Tumors of the Gastrointestinal Tract. Case Report, *Am J Surg* 58:275, 1942.

304 Uihlein, A., and McDonald, J. R. Primary Carcinoma of the Appendix Resembling Carcinoma of the Colon, *Surg, Gynec & Obst* 76:711, 1943.

305 Young, E. L., and Wyman, S. Primary Carcinoma of the Appendix Associated with Acute Appendicitis, *New England J Med* 227:703, 1942.

306 Lynch, R. C., and Dixon, C. F. Mucocele of the Appendix. Report of a Case, *Proc Staff Meet, Mayo Clin* 18:182, 1943.

307 Giffin, H. M., McManamy, E. P., and Waugh, J. M. Surgical Significance of Epiploic Appendages, *Arch Surg* 45:351 (Sept) 1942.

308 Harte, M. S. Chronic Partial Intestinal Obstruction Due to Intussusception of an Appendix Epiploica, *Surgery* 13:555, 1943.

309 Myers, R. S., and Zollinger, R. M. Gastrointestinal Symptoms and Inguinal Hernia, *New England J Med* 227:660, 1942.

310 Ackermann, W. Diverticula and Variations of the Duodenum, *Ann Surg* 117:403, 1943.

311 Finney, J. M. T., Jr. Duodenal Diverticula. Their Significance and Treatment, *South Surgeon* 11:543, 1942.

312 Schoen, W. Notes on Clinical Aspects of the Diverticula of the Duodeno-Jejunal Flexure, *Gastroenterologia* 66:90, 1941.

313 Ovens, G. H. C. Acute Diverticulitis of the Jejunum, *Brit J Surg* 30:239, 1943.

314 van Ravenswaay, A. C., and Winn, G. W. Jejunal Diverticula. A Consideration of Clinical Symptomatology and Case Report, *Am J Digest Dis* 10:108, 1943.

symptoms warrant surgical intervention. These authors review the literature, which includes about 230 reported cases of diverticula in this location.

Meckel's diverticulum is a relatively common source of symptoms in children. In adults it is much less frequent, but it may cause symptoms simulating acute appendicitis or may cause important bleeding, much as it does in the younger age group. Such complications are recorded by Heyn and Doehnert<sup>315</sup> and by Servetnick and Nichols,<sup>316</sup> occurring in persons over 20 years of age. Roentgen demonstration and diagnosis of Meckel's diverticulum are not commonly made. One case studied because of obscure gastrointestinal bleeding is reported by Ledoux.<sup>317</sup> Mulsow<sup>318</sup> was able to find only 9 previous case reports of calculi in Meckel's diverticulum. He reports an additional case in which such stones were mistaken for gallstones. The patient complained of several acute attacks of severe abdominal pain. At operation, a large gangrenous Meckel's diverticulum was found impacted with calculi, which were not gallstones.

Few cases of solitary diverticulitis of the cecum with symptoms simulating acute appendicitis have been reported. Baker and Carlile<sup>319</sup> add 2 cases of this condition, and Schnug<sup>320</sup> reports 6 additional cases.

As a cause of serious symptoms, diverticulitis of the sigmoid is by far the most common source. Smithwick<sup>321</sup> discusses in detail the surgical aspects of this condition. On the basis of 2,400 cases with diverticulosis of the sigmoid, he concludes that diverticulitis will develop in about one quarter of the cases. In the series of cases discussed by this author, one fifth of the patients were treated surgically. The dangers and difficulties associated with operation for this condition are discussed in detail. Of various procedures, he advocates the Mikulicz operation with an open, end to end anastomosis. He considers the reported mortality of 11.5 per cent for this operation too high and believes that the mortality should be reduced. Resection with reestablishment of continuity is usually possible, according to his experience. He believes that resection offers the greatest hope for improvement for persons suffering from severe and complicated forms of diverticulitis. Such a conclusion is probably justified, but it is quite possible that modern chemotherapeutic methods may render surgical intervention unnecessary in many of these complicated cases.

The value of a sigmoidoscopic examination in establishing a diagnosis of diverticulosis is not generally appreciated. Jackman and Buie<sup>322</sup> analyzed 400 cases of diverticulosis of the colon. In 150, the diagnosis was made clinically and by roentgen examination, in 8, by clinical and sigmoidoscopic examination. In 160 of the remaining 242 cases, sigmoidoscopy showed or indicated the presence of diverticula. The most valuable single sigmoidoscopic finding, aside from actually seeing the diverticula, is the presence of sacculations. This report is

315 Heyn, W, and Doehnert, H. R. Meckel's Diverticulum. Clinical Aspects and Pathology, *Deut. Militärarzt* 6: 103, 1941.

316 Servetnick, A, and Nichols, H. G. Hemorrhage from Meckel's Diverticulum in an Adult. Report of a Case, *New England J. Med.* 228: 12, 1943.

317 Ledoux, A. C. Meckel's Diverticulum, *Radiology* 38: 728, 1942.

318 Mulsow, F. W. Meckel's Diverticulum Containing Calculi. Case Report, *Am. J. Digest. Dis.* 10: 188, 1943.

319 Baker, J. W, and Carlile, T. Solitary Diverticulitis of the Cecum, *J. A. M. A.* 122: 354 (June 5) 1943.

320 Schnug, E. Acute Diverticulitis of the Cecum, *Surgery* 13: 282, 1943.

321 Smithwick, R. H. Experiences with the Surgical Management of Diverticulitis of the Sigmoid, *Ann. Surg.* 115: 969, 1942.

322 Jackman, R. J, and Buie, L. A. Diverticula of the Colon. Proctoscopy as an Aid in the Diagnosis and Differential Diagnosis, *J. A. M. A.* 121: 1144 (April) 1943.

informative, but I am inclined to agree with the authors' conclusion that diagnosis should rest fundamentally on careful roentgenologic study

A rare complication of diverticulosis, according to Guthrie and Wakefield,<sup>323</sup> may be mesenteric cysts. Twenty-two such tumors were studied histologically by these authors, who believe that these cysts may represent pinched-off diverticula

*Cancer of the Large Bowel*—As elsewhere in the alimentary canal, it has been found possible to produce malignant tumors in animals by carcinogenic substances. Precancerous epithelial lesions, adenocarcinomas and hemangioendotheliomas of the intestinal tract or adjacent structures were produced in mice by White and Stewart,<sup>324</sup> using methylcholanthrene. Oral administration of olive oil and animal fats previously oxidized by heating produced malignant tumors in the digestive apparatus in rats, as reported by Roffo.<sup>325</sup> Frequently the effect did not appear until after two years. As a study of substances capable of producing malignant growth, Roffo compares the absorption curves for the natural and oxidized fats in the ultraviolet region and compares them with those for phenanthrene, cholesterol and irradiated cholesterol. The possible relations between these two groups of curves are discussed.

As in other portions of the digestive tract, the early recognition of malignant lesions still leaves much to be desired. The candid analysis of diagnostic failures in this disease by Shearburn<sup>326</sup> is at once timely and disappointing. Of 100 consecutive patients with cancer of the rectum, only 36 had had adequate rectal examinations prior to admission to the hospital. Because of the frequent incidence of cancer of the rectum and the successful results following early operation, the responsibility of the general practitioner in this regard is clear. That nearly two thirds of 100 patients with this disease had not had an adequate rectal examination is rather appalling, and the author is to be commended for bringing such statistical data to the general reader. Among other pertinent remarks, one is worthy of repetition—that the treatment of recurrent or prolonged diarrhea without rectal examination is to be condemned. An accompanying statement is equally important—namely, that the treatment of hemorrhoids, either by surgical or by conservative measures, without first investigating the upper part of the rectum is also to be condemned.

In a discussion of the complications and causes of mortality of the surgical treatment of carcinoma of the colon and rectum, Garlock, Ginzburg and Glass<sup>327</sup> report an equal degree of carelessness in another section of the country in this particular respect. Between 20 and 25 per cent of patients admitted to the hospital because of carcinoma of the rectum had undergone treatment for hemorrhoids during the preceding two to five months without adequate digital or proctoscopic examination of the rectum. The preoperative and postoperative therapy

323 Guthrie, R. F., and Wakefield, E. G. Mesenteric Cysts, Proc. Staff Meet., Mayo Clin 18 52, 1943

324 White, J., and Stewart, H. L. Intestinal Adenocarcinoma and Intra-Abdominal Hemangio-Endothelioma in Mice Ingesting Methylcholanthrene, J. Nat. Cancer Inst. 3 331, 1942

325 Roffo, A. H. The Development of Malignant Tumors in the Digestive Apparatus After Ingestion of Fat Oxidized by Heating, Prensa méd. argent. 26 619, 1939, Chem. Zentralbl. 1 1550, 1941

326 Shearburn, E. W. Importance of Rectal Examination in the Prognosis of Rectal Carcinoma, J. A. M. A. 119 1410 (Aug. 22) 1942

327 Garlock, J. H., Ginzburg, L., and Glass, A. Complications and Causes of Mortality of the Surgical Treatment of Carcinoma of the Colon and Rectum, Surg., Gynec. & Obst. 76 51, 1943

in such cases, including chemotherapy, intestinal intubation and the management of cardiovascular complications, is treated in detail in this article

The indications for and against surgical treatment of this disease are thoroughly considered by Shedden<sup>328</sup> and by David and Gilchrist<sup>329</sup>. Shedden points out many of the difficulties incident to radical operation on patients of the older age group. He considers extreme obesity a positive contraindication in persons over 70 years of age. This group of patients, which constitutes 17 per cent of his entire series of 166, receives special consideration in a report which is worthy of study. David and Gilchrist disregard adiposity, age, cardiovascular disease, large tumors, enlargement of regional lymph glands and resectable attachment of the tumor to the prostate, rectovaginal septum, uterus or adnexa, bladder or ureter as contraindications to radical operation. Their decision to extend the indications for radical operation, they admit, will increase operative mortality, but it will also, they believe, result in actually a larger number of patients being given a long term cure. Shedden's figures of 80 per cent operability with a 4.4 per cent mortality are excellent. Bowers<sup>330</sup> is in accord with David and Gilchrist in refusing to accept the extensive involvement of adjacent structures as a contraindication for radical operation. Citing individual cases, he reaches the conclusion that neoplastic involvement of the bladder is no reason in itself to withhold radical operation.

Measures directed toward a reduction in postoperative mortality of cancer of the rectum are discussed by Binkley, Abels and Rhoads<sup>331</sup>. Of 65 patients with malignant neoplasms of the colon and rectum, one third had preoperative hypoproteinemia, a lower figure than that found for patients with cancer of the stomach. This incidence increased to 86 per cent after operation. In the discussion of measures directed against this complication, they advocate the use of intravenous plasma protein in the early preoperative period. During the postoperative convalescence, sufficient amounts of dietary nitrogen may be ingested to counteract the postoperative hypoproteinemia. They believe that the correction of this particular abnormality is in great part responsible for the decreased mortality among patients with rectal and colonic cancer. The presence of infection in the patients studied considerably impaired the effectiveness of the measures outlined to combat the hypoproteinemia.

The palliative treatment of inoperable patients usually resolves itself into intensive radiotherapy. Philips<sup>332</sup> discusses the roentgenotherapy of 65 surgically rejected carcinomas of the rectum. Nineteen tumors disappeared after treatment by million-volt x-rays. Nothing approaching this was seen after treatment with ordinary 200 kilovolt x-rays.

In a study of the gross and microscopic characteristics of carcinoma of the gastrointestinal tract with relation to the incidence of metastases to regional lymph nodes, Kay<sup>333</sup> demonstrated such metastases in two thirds of 53 speci-

328 Shedden, W. M. Cancer of the Rectum and Sigmoid, with Special Reference to the Disease as Seen in Old Age, *Am J Roentgenol* **47** 916, 1942.

329 David, V. C., and Gilchrist, R. K. A Consideration of the Contraindications for Radical Operation in Cancer of the Rectum, *Surgery* **12** 310, 1942.

330 Bowers, R. F. Surgical Treatment of Malignant Lesions of the Sigmoid with Extension, *Ann Surg* **115** 986, 1942.

331 Binkley, G. E., Abels, J. C., and Rhoads, C. P. Treatment of Postoperative Hypoproteinemia in Patients with Cancer of the Colon and Rectum, *Ann Surg* **117** 748, 1943.

332 Philips, R. Discussion on the Treatment of Inoperable Carcinoma of the Rectum, *Proc Roy Soc Med* **35** 768, 1942.

333 Kay, E. B. Regional Lymphatic Metastases of Carcinoma of the Gastro-Intestinal Tract, *Surgery* **12** 553, 1942.



mens removed for rectal cancer. A study of these and of other carcinomas involving the colon and stomach substantiates the conclusion that neoplasms in younger persons tend to have a higher incidence of metastases. There was no relation between the duration of symptoms and the presence of metastases to lymph nodes. No relation was found to exist between the size of the neoplasm and its spread.

The importance of removal of appendices epiploicae in the near vicinity of sigmoidal cancer is stressed by Gilchrist and David,<sup>334</sup> who studied a large number of specimens of carcinoma of the rectum and sigmoid. By injection preparations, lymph channels were demonstrated in the subserosa on the anti-mesenteric border of the sigmoid, which may travel at least 3 cm lengthwise of the bowel before turning laterally to drain into the mesentery. If there are appendices epiploicae in this area, the lymph channel may drain directly into the lymph nodes that they contain. The authors point out that at least 3 cm of sigmoid proximal to a carcinoma must be resected if satisfactory results are to be obtained.

Epidermoid carcinoma of the anus and rectum constitutes a relatively small proportion of malignant rectal or anal neoplasms. Cattell and Williams<sup>335</sup> state its incidence to be 17 per cent and discuss in detail the various therapeutic measures that are indicated.

*Other Tumors of the Large Intestine*—Symptoms of obstruction or hemorrhage are the usual concomitants of a tumor of the large intestine, even when it is benign. Massive hemorrhage may occur even from a submucous lipoma, and a case of such involving the ascending colon is reported by Saint.<sup>336</sup> The frequency with which benign tumors may be found in the large bowel is indicated in a report by Helwig,<sup>337</sup> who demonstrated 154 tumors in 1,460 consecutive autopsies. Of these, 139 were benign adenomas, although the designation of such tumors as benign is somewhat misleading, inasmuch as they represent potential malignant growth. Only 80 of the adenomas occurred as single lesions. There were 13 lipomas in the series. The most common site for the adenomas was found to be the sigmoid colon.

Familial polyposis of the colon is well recognized, although occasionally no history can be obtained of involvement of other members of the family. The case reported by Elkan<sup>338</sup> and 2 of the 3 cases recorded by Pickworth<sup>339</sup> fail to show any history of family involvement, although Elkan states that this condition is inherited as a mendelian dominant. The more usual picture is illustrated in a report by Falk,<sup>340</sup> who presents the study of a family of 7 children 6 of whom showed multiple polyposis of the colon, of whom 2 died after carcinomatous degeneration. The inheritance was from the paternal side, the father dying at 48 of cancer of the rectum and the grandfather at 30 of a severe intestinal condition, which may have been associated with polyposis.

334 Gilchrist, R. K., and David, V. C. Carcinoma Metastases in Appendices Epiploicae. *Surgery* **13** 574, 1943.

335 Cattell, R. B., and Williams, A. C. Epidermoid Carcinoma of the Anus and Rectum, *Arch Surg* **46** 336 (March) 1943.

336 Saint, J. H. Chronic Intussusception Due to Submucous Lipoma of Ascending Colon. Case Report, *Am J Surg* **58** 414, 1942.

337 Helwig, E. B. Benign Tumors of the Large Intestine. Incidence and Distribution. *Surg., Gynec. & Obst* **76** 419, 1943.

338 Elkan, R. E. A Case of Polyposis Intestini, *Brit J Surg* **30** 387, 1943.

339 Pickworth, M. E. Multiple Adenomatosis of the Colon. Case Reports, *Am J Surg* **58** 254, 1942.

340 Falk, V. S. Familial Polyposis of the Colon, *Arch Surg* **45** 123 (July) 1942.

Polyposis involving both the small and the large intestine is almost unique. Gerwig and Stone<sup>341</sup> report such an occurrence in a man of 25, who showed polypoid involvement of the jejunum as well as the colon. Jejunal intussusception was the immediate cause for hospitalization.

Less common tumors of the colon may be mentioned briefly. Stout<sup>342</sup> was able to find but 6 cases of carcinoid of the rectum reported in the literature. He adds 6 additional cases, the histologic features of which differ from those of the commoner carcinoids found in the appendix and small intestine. Leiomyoma is more commonly found in the stomach, rarely in the colon. One case of such a tumor is presented by Good<sup>343</sup>. The roentgen studies in this case revealed the same characteristic previously alluded to, namely, preservation of the mucosal relief around the projected tumor. The rectum is the most common site of gastrointestinal melanoma, although this tumor is relatively infrequent. One is described by Goldman and Robillard<sup>344</sup>. Three cases of primary lymphoid tumor of the rectum are reported by Smith,<sup>345</sup> largely because no report of a primary lymphoid tumor in this location resembling internal hemorrhoids could be found in the literature. One of Smith's tumors was a lymphosarcoma, and 2 were benign lymphomas. The diagnosis was made by microscopic examination of the indurated hemorrhoidal tissue removed at operation.

*Intestinal Parasites*—An increasing recognition of the clinical importance of intestinal parasites in this country is apparent in the numerous articles appearing in the literature. Of these, certain ones have been chosen for mention to illustrate the rather universal interest in this type of disorder of the alimentary tract.

Because of the necessity for a simple method that can become part of a routine examination even in small hospitals, Markey and his associates<sup>346</sup> have evolved a reliable, simple and rapid technic for the iron-hematoxylin staining of fecal material for the study of intestinal protozoa. With their method, they claim that it is possible to obtain temporary preparations suitable for diagnosis in less than ten minutes. Hakansson<sup>347</sup> advocates the use of aqueous smears in the examination of feces for intestinal protozoa. He and his colleagues have used aqueous smears extensively at the Naval Medical School, and have found that for certain purposes such a method can be used advantageously in routine examinations and is particularly helpful to student technicians and inexperienced workers. It is suggested not as a substitute for an isotonic saline solution smear, but as an additional method used principally for the two following purposes: (1) to destroy the blastocysts (*Blastocystis hominis*) and thus facilitate the search for and identification of protozoan cysts, and (2) to identify *Dientamoeba fragilis*.

341 Gerwig, W. H., Jr., and Stone, H. B. Enteric Intussusception in Adults, *Surg., Gynec. & Obst.* **76**:95, 1943.

342 Stout, A. P. Carcinoid Tumors of the Rectum Derived from Erspamer's Pre-Enterochrome Cells, *Am. J. Path.* **18**:993, 1942.

343 Good, C. A. Leiomyoma of the Colon, *Radiology* **39**:731, 1942.

344 Goldman, C., and Robillard, G. Malignant Melanoma of the Rectum, *Am. J. Surg.* **57**:352, 1942.

345 Smith, T. E. Primary Lymphoid Tumors of the Rectum Resembling Internal Hemorrhoids. Report of Three Cases, *J. A. M. A.* **121**:495 (Feb. 13) 1943.

346 Markey, R. L., Culbertson, C. S., and Giordano, A. S. Rapid Method for the Staining of Intestinal Parasites, *Am. J. Clin. Path., Tech. Supp.* **7**:2, 1943.

347 Hakansson, E. G. The Use of Aqueous Smears in the Examination of Feces for Intestinal Protozoa, *Am. J. Trop. Med.* **22**:325, 1942.

In Santo Domingo, Ravelo-Barré and Thomen<sup>348</sup> have studied 500 consecutive fecal specimens, of which over 50 per cent were found to contain some species of intestinal protozoa. Only 14 per cent of the stools revealed *Endamoeba histolytica*. *Balantidium coli* is not known to exist in the district studied.

D'Antoni<sup>349</sup> investigated a total of 236 patients in the New Orleans district because of chronic colonic symptoms, including dysentery, diarrhea, fever of undetermined origin and vague abdominal pain. Over one fourth of the patients revealed evidence of infestation by *E. histolytica*. The symptoms of all but 3 were cured with diodoquin (5,7-diiodo-8-hydroxyquinoline). In 2 of the 3 cases of therapeutic failure, shigella infection was an associated complication, and it was present in 21 others. In another 21 persons symptoms were attributed to the presence of giardiasis, strongyloidiasis or hookworm infection.

An interesting report is found in a survey by Nickel<sup>350</sup> on amebiasis and hookworm infection in Mississippi on the basis of approximately 50,000 examinations of stools. Hookworm infestation was demonstrated in approximately 25 per cent. *E. histolytica* was found in only 4.4 per cent of the entire group, although other protozoa were present in almost one third of the specimens examined. The total number of specimens represented 1 for every 44 persons in the state. Investigations show that the severity of hookworm infections has apparently been reduced, while the number of people infected has increased.

The importance of giardiasis as a cause of symptoms is still a moot question in the minds of most physicians. For this reason, the report of Ormiston and Wilson<sup>351</sup> on a prolonged outbreak of enteritis associated with this infection is of interest. An outbreak is described which occurred in a group of 51 people housed in a family residence used as a wartime nursery. Eighty-six per cent of the inmates showed symptoms of the disease. *Giardia lamblia* was found in three quarters of the children and adults having loose stools at the time of examination and in only one third of those with normal stools. In four fifths of the children and adults with a history of intermittent or continuously loose stools for some months, the parasite was easily demonstrated. A cure was quickly and successfully effected by the use of quinacrine hydrochloride given in two five day courses. If, as is probable, there is a symptom complex associated with *Giardia* infection in a reasonable number of cases, these symptoms are nonspecific but are more or less characteristic of irritation in the region of the pylorus, prepylorus and duodenum, as Welch<sup>352</sup> points out. He describes in detail the symptoms, laboratory findings and results of roentgen examinations in 13 cases. A point of interest is the fairly constant finding of motor and inflammatory changes in the pyloric and duodenal areas, evidenced by changes in mucosal relief and motor activity. This would seem reasonable in view of the locus of infection usually encountered in this condition. Therapy with quinacrine hydrochloride was entirely satisfactory, as is the usual experience. That *Giardia* may occasionally involve the biliary tract has been recognized for some time. In

348 Ravelo-Barré, M., and Thomen, L. F. Incidence of Protozoan Parasites of the Human Intestine in the District of Santo Domingo, Dominican Republic, *Am J Trop Med* **23** 243, 1943.

349 d'Antoni, J. S. Further Observations on Amebic and Bacillary Colitis in the New Orleans Area, *Am J Trop Med* **23** 237, 1943.

350 Nickel, H. S. Amebiasis and Hookworm Infection as Found in Approximately 50,000 Fecal Examinations in Mississippi, *Am J Trop Med* **22** 209, 1942.

351 Ormiston, G., Taylor, J., and Wilson, G. S. Enteritis in a Nursery Home. Prolonged Outbreak of Enteritis Associated with *Giardia Lamblia* (*G. intestinalis*) Affecting Both Children and Adults in a Nursery Home of Evacuees, *Brit M J* **2** 151, 1942.

352 Welch, P. B. Giardiasis with Unusual Clinical Findings. Preliminary Report, *Am J Digest Dis* **10** 52, 1943.

discussing Welch's article, Swalm reports 1 case of giardiasis which was originally diagnosed as carcinoma of the liver. Because of the finding of *Giardia* in the duodenal contents, quinacrine therapy was instituted, and the size of the liver was reduced following therapy. Dreyfuss<sup>353</sup> also refers to involvement of the hepatic parenchyma.

Pinworm (*Enterobius vermicularis*) infection is described in articles by Headlee<sup>354</sup> and Jones<sup>355</sup>. The latter confirms previous reports that there is a decided difference between infection in white persons and in Negroes. In a selected group that was composed of equal numbers of white and of Negro children, the incidence among the white children was 88 per cent, as contrasted with an incidence of only 12 per cent in the Negro group. Diagnoses were made by the NIH swab technic.

An unusual cause for diarrhea is to be found in the report by Ross<sup>356</sup> who describes a patient of 28 who had had intermittent and serious diarrhea since the age of 5. In the absence of other ascertainable cause for the symptom, the relief of the diarrhea after partial destruction of the parasites and the observation by sigmoidoscopy of a worm with its head apparently buried in an inflamed area of colonic mucosa, the author was convinced that the diarrhea was a result of infection by whipworm (*Trichocephalus trichiurus*).

Allusion has already been made to an alteration in the mucosa of the human being secondary to hookworm infection. A detailed study of roentgenologic changes in the small intestine associated with the presence of hookworm is found in an article by Krause and Crilly<sup>357</sup>. These authors describe changes in the small intestinal pattern which are frequently attributed to deficiency disease. Complete studies of the small intestine were made on 97 white men known to harbor hookworm (*Necator americanus*). There was no other disease known to be associated with the hookworm infection. Of 44 patients with clinically significant hookworm disease, 40 showed abnormality of the small intestinal pattern, and in more than half of these the changes were moderately or far advanced. Of the asymptomatic patients, the vast majority had normal roentgen pictures. After anthelmintic therapy, there was a return toward a normal pattern in the cases of severe involvement. The authors suggest, on the basis of previous work by McKenzie in 1939 that such changes are associated with real deficiency disease resulting from impaired absorption.

A thorough examination of 210 appendixes was made by Rector,<sup>358</sup> who made the rather surprising observation that practically 5 per cent were found to be infected with *Oxyuris vermicularis*.

Chandler<sup>359</sup> records the first case to be reported of human infection with tapeworms of the genus *Mesocestoides*. The human infection was probably derived from eating improperly cooked flesh of a wild mammal or possibly a frog.

353 Dreyfuss, P. R. Clinical Observation on Lamblia, *Gastroenterologia* 66:323, 1942.

354 Headlee, W. H. Pinworm Infections Among Patients of an Indiana Hospital for Children, *Am J Trop Med* 23:281, 1943.

355 Jones, E. C. Incidence of Pinworm Infection in White and in Negro Hospitalized Children, *Am J Dis Child* 64:803 (Nov) 1942.

356 Ross, D. S. Chronic Diarrhea Due to *Trichocephalus Trichiurus*, *Lancet* 2:97, 1942.

357 Krause, G. R., and Crilly, J. A. Roentgenologic Changes in the Small Intestine in the Presence of the Hookworm, *Am J Roentgenol* 49:719, 1943.

358 Rector, L. E. Factors Influencing the Reported Incidence of Appendiceal *Oxyuriasis*, *Am J Trop Med* 23:369, 1943.

359 Chandler, A. C. First Record of a Case of Human Infection with Tapeworms of the Genus *Mesocestoides*, *Am J Trop Med* 22:493, 1942.

McCoy<sup>360</sup> submits a rather interesting set of observations concerning the incubation period of trichinosis. Data compiled from the recent literature and from the Rochester (N. Y.) outbreak of 1937 indicate that the incubation period in 156 cases of trichinosis was twenty-two days or less, with rare exceptions. The shortest period was two days. The great variability in the duration of the incubation period and the fact that occasionally it was three weeks or longer emphasize the lack of close correlation between the life cycle of the parasite and the clinical course of the disease. These observations contribute evidence for the view that the symptoms of trichinosis result mainly from an accumulated toxemia, rather than directly from the activities of the parasite during migration in the body.

Sisk<sup>361</sup> reports his experiences in the use of phenothiazine in the treatment of various parasitic infections. This drug is a new preparation distantly related to sulfanilamide, and is the parent substance of a large number of dyes, one of which is methylthionine chloride (methylene blue). Using varying doses, Sisk found that apparently satisfactory results were obtained from a total dose of 12 Gm. for adults over a five day period. The drug was of no appreciable value in the treatment of hookworm or trichuris infection, but apparently was of some value in the treatment of infection due to *Ascaris*.

*Ulcerative Colitis*.—Nothing new of importance can be found in the current literature regarding the cause of this distressing condition. A number of studies are of interest, however, regarding the clinical manifestations of the disease and its treatment. A certain amount of careful attention has been paid to the nutritional factors that are invariably encountered in patients with anything but the mildest forms of ulcerative colitis. Page and his colleagues<sup>362</sup> have carried out a comparative study of dextrose and dextrin tolerance in patients with this disease. Reports by previous authors indicate low or flat blood sugar curves for oral dextrose tolerance tests. In a control group of 58 patients, 40 per cent showed curves of this type. Groen (1938) ascribed the decreased absorption of dextrose to a defect in the absorptive capacity of the intestinal wall, rather than to unusually rapid passage of the intestinal contents. In this particular study, 23 patients with chronic ulcerative colitis of one or more years' duration were investigated. At all points the blood sugar levels were higher after administration of dextrans than of dextrose. One hour after administration of dextrose the true blood dextrose had risen 42 per cent over the average fasting level, while after the administration of dextrin it had increased 70 per cent. Two hours after administration of dextrin the blood sugar level was 21 per cent above normal, as compared with a 7 per cent elevation for dextrose. At the end of three hours the levels were essentially the same with the two test substances.

Zetzel, Banks and Sagall,<sup>363</sup> using a previously described technic, estimated the rate of absorption of amino acids from a closed jejunal loop in 3 patients with chronic idiopathic ulcerative colitis and in 2 with chronic enterocolitis. All were studied during an exacerbation of the disease. In 4 cases there was marked impairment of absorption as compared with that of normal persons. The degree of

360 McCoy, O. R. Incubation Period of Trichinosis, *Am J Trop Med* **22** 313, 1942

361 Sisk, W. N. Effect of Phenothiazine on Intestinal Parasites, *J. A. M. A.* **122** 357 (June 5) 1943

362 Page, R. C., Bercovitz, Z., and deBeer, E. J. A Comparative Study of Dextrose and Dextrin Tolerance in Patients with Chronic Ulcerative Colitis, *J. Lab & Clin Med* **28** 66, 1942

363 Zetzel, L., Banks, B. M., and Sagall, E. Intestinal Absorption of an Amino-Acid Mixture in Patients with Chronic Idiopathic Ulcerative Colitis and Entero-Colitis, *Am J Digest Dis* **9** 350, 1942

impairment of absorption was correlated with the severity of clinical evidence of malnutrition, as shown by the case reports. The authors mention the possibility that incomplete digestion also occurs in the small intestine of patients with chronic ulcerative colitis, but they feel that the results of their study and of previous ones by Elsom indicate that dysfunction of the small intestine contributes to the development of the deficiency states seen in the disease. The derangement of absorption contributes to the clinical manifestations by perpetuating a vicious cycle in spite of adequate oral intake, and therefore parenteral administration of essential and accessory food factors is important. It is highly probable that these evidences of dysfunction of the small bowel in ulcerative colitis are indicated in part by the frequent abnormalities noted during roentgenologic examination. These changes for the most part are reversible.

Page and Bercovitz<sup>364</sup> continue their studies on vitamin A absorption in chronic ulcerative colitis by determining the vitamin A level in the blood plasma before and after the oral administration of 100,000 U S P units of vitamin A. Twenty-five patients with chronic ulcerative colitis, 9 patients with miscellaneous diseases of the digestive tract and 8 normal controls were investigated, and the expected result was obtained—that the plasma vitamin A level did not rise so high in patients with ulcerative colitis as in the control subjects.

It is generally recognized that prothrombin deficiency is a frequent finding in this disease. Continuing their studies on the deficiency aspects of the condition, Page and Bercovitz<sup>365</sup> determined the prothrombin clotting time and the fibrinogen content of the blood plasma in 21 patients. Six had a constant hypoprothrombinemia, and 13 additional patients fluctuated between normal and slightly prolonged prothrombin clotting times during the period of study, which covered twenty-one weeks. The figures for plasma fibrinogen, as a rule, were slightly higher than in normal adults, and the authors rightly conclude that the low blood prothrombin level offers the best explanation for the deficiency factor concerned with colonic bleeding.

Other nutritional disturbances have been generally recognized in this condition, and it is a common experience to encounter evidences of retarded or abnormal sexual or somatic function in these patients. Benson and Barger<sup>366</sup> discuss in detail developmental changes or retardation, with particular reference to the formative years of childhood and adolescence, on the basis of 14 cases referred because of the erroneous suspicion that the patients were suffering from infantilism of pituitary origin or dwarfism. In all of the patients, development and growth had been normal up to the onset of symptoms of colitis, and the symptoms of infantilism are entirely in keeping with the amenorrhea observed in women with this condition. These changes are in all probability associated with faulty steroid metabolism secondary to impaired absorption.

Taking as a subject the management of ulcerative colitis, Barger<sup>367</sup> discusses the various conditions producing ulceration in the colon which can be grouped under this heading. So-called thromboulcerative colitis or idiopathic ulcerative colitis, regional ulcerative colitis and ulcerative colitis due to tuberculosis, venereal

364 Page, R. C., and Bercovitz, Z. Absorption of Vitamin A in Chronic Ulcerative Colitis, *Am J Digest Dis* 10 174, 1943.

365 Page, R. C., and Bercovitz, Z. Prothrombin and Fibrinogen Studies in Chronic Ulcerative Colitis, *Am J Digest Dis* 9 419, 1942.

366 Benson, R. E., and Barger, J. A. Chronic Ulcerative Colitis as a Cause of Retarded Sexual and Somatic Development, *Gastroenterology* 1 147, 1943.

367 Barger, J. A. The Management of Ulcerative Colitis, *Gastroenterology* 1 449, 1943.

lymphogranuloma, bacillary dysentery, dietary insufficiency and allergic disorders are all discussed in detail. Because of the magnitude of his experience with this condition, the article is well worth reading and is presented in an authoritative fashion, although there is nothing particularly new in it. With the exception of the fact that the author clings to the idea that a characteristic streptococcus is the cause of thrombolytic colitis no exception can be taken to this splendid article. Diagnostic, clinical and therapeutic features of the disease are well summarized.

Chemotherapy for this condition is still on trial, and a variety of opinions regarding its efficacy are to be found in the current literature. Mills and Mackie<sup>368</sup> describe the condition as a polyvalent disease, the primary cause of which is imperfectly understood and the fundamental pathogenesis of which is nonspecific infection of the colon with any of a variety of organisms of mixed pathogenicity. The vast majority of experienced observers would agree with this definition. The paper of Mills and Mackie deals with the use of sulfathiazole, sulfaguanidine and sulfadiazine in 109 unselected cases. Definite or marked improvement was obtained in 78 per cent of the cases. Sulfadiazine proved to be the drug of choice for all varieties. Sulfaguanidine was of definite benefit in the majority of cases without excessive diarrhea. The authors are careful to point out that none of these drugs should be considered specific for the disease, and no patient should be considered cured by chemotherapy.

Kirsner and his associates<sup>369</sup> report the treatment of 20 patients suffering from ulcerative colitis, venereal lymphogranuloma, bacillary dysentery and miscellaneous intestinal infections. Sulfaguanidine was used, and these authors, unlike the preceding ones, found no value from therapy with this drug in cases of nonspecific ulcerative colitis. They feel that the drug is of no value in the treatment of paratyphoid B infection and that it has no advantage over other sulfonamide compounds in the treatment of lymphogranuloma venereum. Like all other investigators, the same authors<sup>370</sup> noted that this and other sulfonamide compounds decrease the bacterial count of the feces and transform the fecal flora from one with a predominance of coliform bacilli to one composed almost entirely of gram-positive organisms.

Succinylsulfathiazole, because of its relatively slight absorption from the gastrointestinal tract, was chosen by Crohn<sup>371</sup> for trial in the treatment of 37 patients with intestinal inflammatory diseases, of whom 28 had nonspecific ulcerative colitis, 8 ileitis and 1 actinomycosis of the bowel. The doses employed were those originally described by Poth and were given over two periods of ten days each, with an interval of five days between. The patient with actinomycosis, with several fistulas, showed definite improvement. None was noted in the patients with ileitis. Crohn was impressed, however, by the results obtained in the patients with ulcerative colitis, 5 of whom showed a quick symptomatic cure and 11 more definite improvement. [ED NOTE—This is not entirely in keeping with my experience in following a number of such patients during sulfasuxidine therapy. Only those

368 Mills, M. A., and Mackie, T. T. Chemotherapy of Chronic Ulcerative Colitis, *Am J Digest Dis* 10 55, 1943.

369 Kirsner, J. B., Rodaniche, E. C., and Palmer, W. L. The Use of Sulfaguanidine in Non-Specific Ulcerative Colitis and Other Infections of the Bowel, *Am J Digest Dis* 9 229, 1942.

370 Rodaniche, E. C., Kirsner, J. B., and Palmer, W. L. Effect of the Oral Administration of Sulfonamide Compounds on the Fecal Flora of Patients with Non-Specific Ulcerative Colitis, *Gastroenterology* 1.133, 1943.

371 Crohn, B. B. The Clinical Use of Succinyl Sulfathiazole (Sulfasuxidine), *Gastroenterology* 1 140, 1943.



without fever have been benefited, and they only after the prolonged administration of the drug, an experience contrary to that of Clohn, who claims the best results in the cases of acute colitis [C M J]

A new sulfonamide compound, salicylazosulfapyridine, has been used in a few cases by Svartz,<sup>372</sup> who considers the drug to be the best available medicament against ulcerative colitis. The group studied is rather small, and the fact that fever and cutaneous rashes were frequently encountered would seem to militate against the use of this particular compound.

Neumann<sup>373</sup> suggests a new therapeutic approach to the problem of ulcerative colitis, namely, pneumoperitoneum. The improvement claimed is ascribed in part to activation of the visceral peritoneum and "tuning it to a higher pitch" by setting up a permanent balance irritation to the vast peritoneal surface, and in part to mechanical action and influence on the autonomic nervous system. That such a measure might be of real help in cases of apparently intractable chronic ulcerative colitis is interesting if true.

A discussion of ileostomy as a therapeutic measure for ulcerative colitis is given by Bergen and his colleagues,<sup>374</sup> but their conclusions and comments are in the main biased by a predilection for medical therapy. Their statement that ileostomy should be reserved for those patients who have complications and for the occasional patient who has intractable ulcerative colitis would meet with general approval. Intractability, however, should include prolonged inadequacy as regards general nutrition and ability to lead a normal life. When these criteria cannot be met, most experienced clinicians favor ileostomy over semi-invalidism under medical therapy. In the discussion of the complications following ileostomy, all of the various associated sequelae are clearly described. There is an implication (which seems unfortunate) that many of these are complications of the ileostomy rather than of the underlying disease.

A more reasonable list of indications for ileostomy in this chronic disease is presented by Cattell,<sup>375</sup> who believes that the operation should be performed in cases of acute, fulminating ileitis, whether in the first or in recurrent attacks, on patients for whom medical treatment has failed, including those patients who are incapacitated, and on patients with massive hemorrhage, subacute perforation, abscess, peritonitis or fistulas, obstruction or polyposis, including those with possible cancer. Except for the first indication listed, namely, acute fulminating attacks, most clinicians would be in accord. Experience with ileostomy has been unsatisfactory in most instances in which operation was performed because of an acute fulminating attack. Cattell cites 9 instances in which ileostomy openings have been closed and gives what are usually considered adequate indications for such a decision. These are: clinical remission of symptoms over an appreciable period, healing or inactivity of the inflammatory process observed by sigmoidoscopy, demonstration that the colon is distensible by means of a barium sulfate enema or a double contrast air enema.

*Gastrointestinal Disturbances in Children*—Gastrointestinal symptoms noted in the newborn infant and in children possess some peculiarities that warrant comment.

372 Svartz, N. Treatment of Ulcerative Colitis by Salicylazosulfapyridine, *Gastroenterologia* **66** 312, 1942.

373 Neumann, H. Treatment of Chronic Ulcerative Colitis by Pneumoperitoneum, *Brit M J* **1** 9, 1943.

374 Bergen, J. A., Lindahl, W. W., Ashburn, F. S., and Pemberton, J. deJ. Ileostomy for Chronic Ulcerative Colitis (End Results and Complications in 185 Cases), *Ann Int Med* **18** 43, 1943.

375 Cattell, R. B. Closure of Ileostomy in Ulcerative Colitis, *Ann Surg* **115** 956, 1942.

under a separate heading. On the basis that no other group of persons so nearly approaches the healthy state as do newborn infants, Henderson<sup>376</sup> made roentgen studies on a group of 100 babies 9 days old or under. The esophagus was sometimes fusiform and sometimes straight, the lower half nearly always distending to a greater size than the upper half. Various modifications of the adult shape of the stomach were noted, but it is interesting to realize that many of the subjects presented the phenomenon of cascading. The size of the stomach varied with the amount of air swallowed. Pylorospasm was seldom encountered. The emptying time was definitely slower than that noted in older persons, the stomach being clear of barium at the end of eight hours in only 30 of 110; in some there was twenty-four hour stasis. Segmentation was normal at a level below the duodenum, but the jejunal markings were frequently those beaded and stringlike. Only a few children were reexamined at a later age, but in each the emptying of the stomach was more rapid than at the first examination.

Histologic studies of the stomach and the small intestine in fetuses and in infants dying at birth were made by Bouslog,<sup>377</sup> who noted that all the characteristic subdivisions of the adult were present in the stomachs examined but that muscular development was lacking. The duodenum appeared more like a tube and did not show the divisions of the adult duodenum. The jejunum and ileum were less developed than in the adult. These findings are entirely consistent with the motor phenomena just alluded to.

Zwerling and Nelson<sup>378</sup> studied the roentgenologic pattern of the small intestine in infants and children ranging from 3 months to 11 years of age. The results of the study showed wide variations in the pattern, which led the authors to an important conclusion, namely, that the roentgen appearance of the small intestine is not at the present time a reliable criterion for the diagnosis of nutritional deficiency states.

Henderson and Briant<sup>379</sup> also record observations made after barium sulfate enemas on 105 healthy infants under 9 days of age. Haustrations were present but were more shallow and less numerous than in older infants and adults. The sigmoid was always redundant, and redundancy of the descending colon, splenic flexure, transverse portion of the hepatic flexure and ascending colon was frequently found.

Freudenberg<sup>380</sup> reviews the subject of severe vomiting in infancy and presents a discussion of the differential diagnoses to be considered during the first few days of life. Malformations should be considered first and should include atresia of the esophagus and suprapapillary and infrapapillary stenosis of the duodenum. After ten days of life, pyloric stenosis, cardiospasm and esophageal spasm should be looked for, and after six to twelve months, rumination in neuropathic infants.

For those interested in the problem of infantile pyloric stenosis with particular reference to surgical treatment, a complete review of the subject is presented by

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376 Henderson, S. G. The Gastrointestinal Tract in the Healthy Newborn Infant, *Am J Roentgenol* **48** 302, 1942.

377 Bouslog, J. S. The Normal Stomach and Small Intestine in the Infant, *Radiology* **39** 253, 1942.

378 Zwerling, H., and Nelson, W. E. The Roentgenologic Pattern of the Small Intestine in Infants and Children, *Radiology* **40** 277, 1943.

379 Henderson, S. G., and Briant, W. W. The Colon in the Healthy Newborn Infant, *Radiology* **39** 261, 1942.

380 Freudenberg, E. Severe Vomiting in Infancy, *Schweiz med Wchnschr* **72** 405, 1942.

Szilagyı and McGraw<sup>381</sup> In the discussion of medical treatment of pyloric stenosis, Engel's article<sup>382</sup> is of interest in that, unlike many observers, he states that atropine methylnitrate is of no reliable help. He believes that surgical methods are always to be preferred if it is desirable to shorten the duration of treatment, particularly if undernourishment is present.

Although it was originally described by Cruveilhier, little recognition is made generally of the occurrence of peptic ulcer in infancy and childhood. Guthrie<sup>383</sup> reviews the literature on this particular type of ulcer and records in detail the observations in 9 cases with autopsy. Histologic examination of the ulcers suggested that they developed rapidly and proved fatal before there was time for the occurrence of any noteworthy cellular reaction. Of the patients studied, 6 were under 3 months of age, and 1 of these died when 3 days old. Potential etiologic factors are discussed, such as circulatory instability following prolonged labor and umbilical sepsis, but this discussion is purely speculative. The author makes the important point that hemorrhage from the stomach or bowel is the most characteristic sign of peptic ulcer in infants. Franklin<sup>384</sup> reports 2 cases of duodenal ulcer in children, of whom 1 had gross hemorrhage. Like other observers, Moore<sup>385</sup> comments on the diversity of symptoms in children and stresses the occurrence of pain and tenderness suggesting acute appendicitis as a not uncommon condition. Clyne and Rabinowitch<sup>386</sup> also stress this point, citing their experiences with 4 children ranging from 5 to 13 years. Only in the latter did the symptoms in any sense resemble those of typical peptic ulcer in adults. Newman<sup>387</sup> reports the cases of 6 patients, ranging from 4½ to 12 years of age and again stresses the fact that symptoms are atypical. Because of this fact the diagnosis of peptic ulcer in infants and children is basically a roentgenologic one, and the possibility should always be borne in mind when obscure abdominal pain is encountered in a child.

Reports on the occurrence and treatment of appendicitis in infants and children present nothing new but emphasize the fact that at times the clinical picture is extremely atypical. Such a case is reported by Emerson,<sup>388</sup> who also reviews the literature and cites a successful operation for acute appendicitis in an infant 3 months old. He stresses two important points—the insidious onset of the condition and the rapidity of its progress to gangrene and perforation. In the differential diagnosis, he stresses the generally well recognized fact that not infrequently a pleural or pneumonic infection can easily simulate the picture of appendicitis.

In areas where dysentery is usually mild and precautions against its spread are not normally so rigorous as those against typhoid, hospital diarrhea still affects thousands of children, with many fatalities. This has been accentuated by the use of emergency hospitals in England, for example, since the outbreak of the war. Evans<sup>389</sup> describes the experience of one such hospital in the last three years.

381 Szilagyı, D. E., and McGraw, A. B. The Problems of Infantile Pyloric Stenosis with Particular Reference to Surgical Treatment. A Survey of the Pertinent Literature and a Clinical Analysis of Thirty-Four Cases, *Surgery* **13** 764, 1943.

382 Engel, S. Medical or Surgical Treatment of Pyloric Stenosis, *Brit J Child Dis* **39** 72, 1942.

383 Guthrie, K. J. Peptic Ulcer in Infancy and Childhood, with Review of the Literature, *Arch Dis Childhood* **17** 82, 1942.

384 Franklin, A. W. Two Cases of Duodenal Ulceration in Children, *Arch Dis Childhood* **17** 95, 1942.

385 Moore, O. M. Peptic Ulcer in Children, *Canad M A J* **44** 462, 1941.

386 Clyne, D. G. W., and Rabinowitch, J. Four Cases of Duodenal Ulcer in Children Simulating Acute Appendicitis, *Arch Dis Childhood* **17** 102, 1942.

387 Newman, A. B. Peptic Ulcer in Childhood, *Am J Dis Child* **64** 649 (Oct) 1942.

388 Emerson, A. H. Acute Appendicitis in Infancy, *Am J Surg* **59** 563, 1943.

389 Evans, P. Hospital Diarrhoea, *Arch Dis Childhood* **17** 130, 1942.

Among approximately 2,000 children admitted, of whom nearly 500 were under 2 years of age, there were 203 attacks of diarrhea starting after admission to the hospital. Of the epidemic attacks, 89 were due to bacillary dysentery, 68 to food poisoning and 33 to other causes. It is of interest that 10 of the nurses in the institution had Sonne dysentery. The author suggests four reasons for the spread of what is obviously a preventable disease: delayed diagnoses, inadequate bacterial studies, incontinence in children and lack of proper nursing facilities. The lessons to be drawn from his report are correct. McClure<sup>390</sup> describes four epidemics of infectious diarrhea of newborn infants, with particular relation to the bacteriologic findings. The hemolytic colon organisms appeared to show a much greater incidence in infants having epidemic diarrhea than in well infants in the same nursery. In the epidemics investigated, the most toxic strains were isolated in a fatal case, whereas toxins isolated from an infant with loose stools in a milder epidemic produced milder symptoms. This author stresses the close association between the complementary feedings and the bathing and changing of the infants as a potent source in the spread of this infection. Felsen and Wolarsky<sup>391</sup> report a small epidemic in which the most striking bacteriologic finding was a pure culture of *Staphylococcus aureus*. No single agent was demonstrated, however, and they express the belief that epidemic diarrhea of the newborn may be a form of "focal nonspecific enterocolitis." Plasma was found to be a valuable therapeutic agent. The importance of bacteriologic studies in cases of so-called "summer diarrhea" is stressed by Kazarnovskaya and Soloveva,<sup>392</sup> who believe that a large number of all conditions clinically diagnosed as hemorrhagic colitis are really bacillary dysentery. Chemotherapy for infants with diarrhea varies little from that employed for adults and will be commented on later.

An interesting discussion of the cause and treatment of celiac disease is to be found in an article by May, McCreary and Blackfan<sup>393</sup>. As these authors have previously noted, the laboratory findings of the celiac syndrome established since Gee's time are: a flat sugar curve in the dextrose tolerance test, clumping of the barium meal in the roentgenogram of the gastrointestinal tract, and excess fat in the feces by chemical analysis. From the data obtained in a study of 40 patients with celiac disease, May and his associates show that benefit was irregular and usually only partial when crude extracts of liver or vitamin B complex were used separately. Definite improvement in the absorption of vitamin A and in the clinical picture was invariably obtained in a relatively short time when both extracts were given in large amounts. There was no evidence as to the means by which absorption in celiac disease was improved by the two extracts. One obvious hypothesis is that some defect in the phosphorylation process in the mucosa is the cause of the impaired absorption, and on such a premise some factor or factors in the crude extracts might be considered to play an indispensable role in phosphorylation. The treatment outlined consisted in alternate daily intramuscular injections of 2 cc of crude liver extract (Lilly) and 4 cc of a preparation of vitamin B complex (parenteral B complex Lederle). These injections were continued for three weeks until definite clinical improvement was observed, after which vitamin B complex

390 McClure, W. B. The Role of Colon Organisms and Their Toxins in Epidemic Diarrhea of the Newborn Infant, *J. Pediat.* **22**:60, 1943.

391 Felsen, J., and Wolarsky, W. Epidemic Diarrhea of the Newborn, *Arch. Pediat.* **59**:495, 1942.

392 Kazarnovskaya, S. S., and Soloveva, O. I. Etiology and Diagnosis of Dysentery in Young Children, *Sovet vrach zhur.* **4**:254, 1941.

393 May, C. D., McCreary, J. F., and Blackfan, K. D. Notes Concerning Cause and Treatment of Celiac Disease, *J. Pediat.* **21**:289, 1942.

was given orally. Patients were maintained on a normal diet from the outset of treatment. The favorable effects of parenterally administered riboflavin in patients with celiac disease and sprue and in a patient with adrenal insufficiency and steatorrhea are considered by Antognini<sup>394</sup> as best explained by the assumption that this vitamin occurs as a phosphorylated compound in the intestine and that in this form it exerts its effect on absorption of fat. The roentgenologic aspects of celiac disease are discussed by Deamer and Capp<sup>395</sup> in a paper dealing with celiac disease and chronic intestinal indigestion other than that associated with cystic fibrotic disease of the pancreas in children 2 to 3 years of age. The disorderly clumping of barium as it progresses through the gastrointestinal tract is described, but one is inclined to accept any diagnostic specificity of such a finding with a certain amount of reservation in view of the control studies already alluded to.

The second case of meconium ileus associated with stenosis of the pancreatic ducts to be reported in the literature is described by Hurwitt and Arnheim<sup>396</sup>. Their record is of interest because of the discussion on the relationship between congenital stenosis of the pancreatic ducts and the resulting meconium ileus, which is assumed to be due to the interference with the passage of pancreatic enzymes into the duodenum. A still more unusual occurrence is described by Agerty and his associates,<sup>397</sup> in which a successful operation for a perforation of the ileum was performed on a premature infant within fifty-six hours after birth. The perforation apparently had occurred in fetal life, inasmuch as a fibrous exudate was noted around the perforated loop at the time of operation. Another rare phenomenon is reported by Morrison and Neville,<sup>398</sup> who cite a case of omphalocele with congenital obstruction occurring at birth. The size of what was a true congenital umbilical hernia increased rapidly within five minutes after birth to a diameter of approximately 12 cm, owing to swallowing of air. The infant was operated on successfully when 80 minutes of age.

The administration of drugs by mouth is frequently impossible in a child because of continued vomiting. In cases of meningitis, pneumonia and bacillary dysentery, for example, some alternative to the oral administration of sulfonamide derivatives is desirable. Zerbino and Norbis<sup>399</sup> discuss the intraperitoneal injection of sulfonamide derivatives in children. When administered by the peritoneal route, such a drug appeared readily, for example, in the cerebrospinal fluid, and the authors advocate such administration when the oral route is not favorable.

*Vitamins*—A complete discussion of the current literature on vitamins in this review is not desirable, but certain articles will be cited that bear on the subject of gastrointestinal physiology or disease. Rao<sup>400</sup> states that monkeys fed on diets based largely on milled rice and containing supplementary food in small quantities,

394 Antognini, R. Steatorrhea and Lactoflavin, *Schweiz med Wchnschr* **71** 510, 1941, abstracted, *Trop Dis Bull* **39** 44, 1942.

395 Deamer, W C, and Capp, C S. Clinical Aspects of Gastrointestinal Disease in Childhood, *Radiology* **39** 273, 1942.

396 Hurwitt, E S, and Arnheim, E E. Meconium Ileus Associated with Stenosis of the Pancreatic Ducts. A Clinical, Pathologic and Embryologic Study, *Am J Dis Child* **64** 443 (Sept) 1942.

397 Agerty, H A, Ziserman, A J, and Shollenberger, C L. A Case of Perforation of the Ileum in a Newborn Infant with Operation and Recovery, *J Pediat* **22** 233, 1943.

398 Morrison, H J, and Neville, R L. Omphalocele with Congenital Obstruction. Report of a Case with Meckel's Diverticulum, *Am J Dis Child* **65** 781 (May) 1943.

399 Zerbino, V, and Norbis, A. Sulfonamide Derivatives for Intraperitoneal Injection in Children, *Arch de pediat d Uruguay* **13** 37, 1942.

400 Rao, M V Radakrishna. Intestinal Changes in Monkeys Fed on Poor Rice Diets, *Indian J M Rsearch* **30** 273, 1942.

similar to those consumed by the poor rice eaters in southern India had chronic diarrhea accompanied by atrophic changes in the small intestine. Histologic examination showed varying degrees of degenerative changes in the different layers of the intestine and in the intramural nerve plexus. These changes did not occur in animals fed on a good diet based on whole wheat, milk and vegetables. In both groups, inflammatory lesions resulting from a superimposed bacillary dysenteric infection were sometimes present in the large bowel. Such changes are characteristically found in fatal cases of pellagra but are not found in sprue. A study by Ingelfinger and Moss<sup>401</sup> on patients with sprue is therefore of interest. Records of the motor activity of the small intestine were repeatedly taken for 2 patients with sprue. These records showed that the intestine in sprue lacks the resistance to distention exhibited by the normal intestine, that L waves are only intermittently present and that S waves tend to be of small amplitude. Treatment over short periods with individual fractions of the vitamin B complex produced little change in the tracings, prolonged treatment with whole vitamin B complex produced some improvement only, and this improvement was not commensurate with the clinical results obtained. Injections of acetylbetamethylcholine chloride stimulated intestinal motility, but prostigmine was without effect. In 1 patient posterior pituitary solution, adrenal cortical extract and desoxycorticosterone produce no change. These observations suggested to the authors that in sprue the nervous apparatus of the small intestine fails to liberate active acetylcholine.

In experiments on animals Martin and his collaborators<sup>402</sup> made a study of the influence of single and multiple B complex deficiencies on the motility of the gastrointestinal tract. Various combinations of dietary deficiencies were produced, in which one or another component of the B complex was omitted. The authors were convinced from their results that both inositol and pantothenic acid are associated with the maintenance of normal gastrointestinal motor function. The striking similarity of their deficiencies in their effect on the digestive tract suggested an interdependence of the two. A deficiency of either resulted in increased gastric emptying time with pylorospasm, marked segmentation of both small and large intestine, general hypertonicity and hypomotility, alternation of ribbonlike segments with dilated loops, frequent formation of gas, and fluid levels.

The factors concerned in the so-called deficiency pattern noted by roentgenologists in the small intestine is discussed by Sussman and Wachtel<sup>403</sup>. They make the important point that edema and infiltration of the submucosa, atrophy of the mucosa, muscular damage, and neural degeneration, modified at times by abnormal intestinal content and by unusual hormonal or nervous stimuli, individually are sufficient to produce this deficiency pattern. With some diseases, such as granulomatous jejunoileitis and allergic enteritis, there is no reason to suspect that any other factors are operating. In nutritional deficiency, a primary disturbance in the tissues may be produced by the deficiency itself, which seems to be related to the lack of certain vitamin B components. Golden, in discussing this article, insists on the importance of considering that the common denominator in all of these conditions is a pathologic or physiologic disturbance within the intestinal wall. Some of the possible contributing factors have been presented.

401 Ingelfinger, F. J., and Moss, R. E. The Motility of the Small Intestine in Sprue, *J. Clin. Investigation* **22** 345, 1943.

402 Martin, G. J., Thompson, M. R., and de Carvajal-Forero, J. The Influence of Single and Multiple B Complex Deficiencies upon the Motility of the Gastro-Intestinal Tract, *Am. J. Digest. Dis.* **9** 268, 1942.

403 Sussman, M. L., and Wachtel, E. Factors Concerned in the Abnormal Distribution of Barium in the Small Bowel, *Radiology* **40** 128, 1943.

The results of experiments bearing on the absorption of ascorbic acid from the upper part of the small intestine are fully described by Nicholson and Chornock<sup>404</sup> Using intubation methods, these observers established the fact that if one estimates the absorbing power of the entire small intestine for this vitamin, from the figures obtained in their experiments (for a 45 cm segment over one hour) it is obvious that 20 to 40 Gm can be taken up within twenty-four hours They remark that no exact data are available on the rapidity of the flow that would be necessary to prevent the minimal required uptake of ascorbic acid from intestinal contents containing an average concentration of the substance, but it seems probable that a diarrhea capable of producing scurvy would have to be of great intensity The importance of tissue reserves of ascorbic acid in the healing of wounds is discussed by Lund,<sup>405</sup> with particular reference to gastrointestinal surgery A total of forty-eight gastric operations were done on 43 patients Few showed evidence of ascorbic acid saturation before treatment Few had had a normal intake or plasma level of ascorbic acid, a normal concentration of ascorbic acid in the white blood cells or a normal reserve In a few, the ascorbic acid reserve was so low that the condition could almost be called scurvy The greatest number had from 20 to 50 per cent of the normal reserve When nonradical operations were performed, there were more complications and deaths in patients with low ascorbic reserves than in those with high Although the conclusions are based on inadequate statistical data, there can be little doubt that the emphasis placed by Lund on adequate immediate pre-operative and postoperative vitamin therapy is important, with particular reference to wound healing and tissue repair

Papillary atrophy of the tongue has been commonly recognized for a long time as resulting from dietary deficiency That the occurrence of oral leukoplakia can be attributed to similar factors is less commonly accepted The study of Abels and his associates<sup>406</sup> is therefore of interest Fifty patients with lesions of leukoplakia of the mouth were examined carefully from the point of view of dietary deficiency, and subsequent therapy with brewers' yeast was instituted There was an occasional complete remission of the leukoplakia lesions in patients thus treated, which suggested that a relationship between such lesions and inadequate intake of certain dietary factors present in yeast is an important one The oral lesions were found, as might have been expected, in varying conditions involving the gastrointestinal tract and the liver

*Amino Acids*—An important consideration in the treatment of disease of the digestive tract is the maintenance or restoration of nitrogen equilibrium The most important contribution has been the use of amino acid preparations by various routes Elman, in particular, by his preparations of hydrolyzed casein, has made such therapeutic measures feasible In his earlier work<sup>407</sup> he and his associates demonstrated the safety with which dextrose solutions containing a mixture of amino acids can be administered to human patients in amounts averaging from 8 to 12 Gm

404 Nicholson, J T L, and Chornock, F W Intubation Studies of the Human Small Intestine An Improved Technic for the Study of Absorption, Its Application to Ascorbic Acid, *J Clin Investigation* **21** 505, 1942

405 Lund, C C Ascorbic Acid Deficiency Associated with Gastric Lesions, *New England J Med* **227** 247, 1942

406 Abels, J C, Rekers, P E, Martin, H, and Rhoads, C P Relationship Between Dietary Deficiency and Occurrence of Papillary Atrophy of Tongue and Oral Leukoplakia, *Cancer Research* **2** 381, 1942

407 Elman, R, Weiner, D O, and Bradley, E Intravenous Injections of Amino-Acids (Hydrolyzed Casein) in Postoperative Patients, *Ann Surg* **115** 1160, 1942



of the amino acids per hour. In a recent article<sup>408</sup> he presents a brief and preliminary report concerning the use of hydrolyzed casein orally or by enterostomy tube for a variety of surgical patients. The observations were divided into three groups. In the first group, patients were studied in whom whole protein by mouth seemed to be inadequately digested, presumably because of nutritional edema of the gastrointestinal tract. Hypoproteinemia was severe in all these patients, and external edema was often visible. Persistent diarrhea indicated clearly the failure of normal digestion and absorption. A second group consisted of patients who could be fed only through a tube emptying directly into the jejunum. Finally, a third group of patients was studied, by whom especially large amounts of protein nourishment were needed in order to correct nutritional deficiency as rapidly as possible. The results of this study showed that absorption and utilization occur under circumstances in which whole protein is ineffective. The use of the hydrolyzed casein seemed to permit the assimilation of much larger daily amounts of protein nourishment than is possible when the whole protein is given. Besides the surgical patients already mentioned, the author believes that other patients would probably also be benefited by this treatment, such as those with hypermobility of the gastrointestinal tract due to many other conditions and those with pancreatic or other enzymic deficiency, in which protein is not normally digested and absorbed.

The value of parenteral nitrogen nutrition by means of casein digest was studied by Brunschwig, Clark, and Corbin.<sup>409</sup> Determinations of nitrogen balance in 41 patients subjected to a variety of major surgical procedures revealed a net loss of nitrogen for the first 10 day period which varied widely, from 3.8 Gm to 175.8 Gm, in 36 patients. This loss of nitrogen was obviously due to the restricted ingestion of food combined with the physiologic disturbances accompanying a major surgical operation. The intravenous administration of casein digest in proper proportion with dextrose is effective in reducing or even preventing postoperative net loss of nitrogen and, as is now becoming generally recognized, constitutes a most important postoperative therapeutic measure.

As pointed out by Shohl,<sup>410</sup> great progress has been made in the treatment of acute gastrointestinal disturbances in infants in the last few decades, but an unsolved problem is the provision of adequate amounts of nitrogen essential for normal nutrition. Twenty infants too ill for outpatient treatment were treated by intravenous or oral administration of casein hydrolysate. The infants were suffering from prolonged vomiting or diarrhea and fever, which led to dehydration and sometimes acidosis of a grade requiring parenteral fluid therapy and withholding of fluid by mouth. They varied in age from 2 weeks to 8 months. These infants were able to retain nitrogen when given in adequate amounts in the form of casein hydrolysate, either intravenously or orally or both. Positive nitrogen balances were obtained when the nitrogen intake was 0.35 Gm per kilogram of body weight per day. Retentions of nitrogen were greater when intakes were greater, and were as large as those reported for well infants.

The minimum maintenance requirement of an enzymic casein hydrolysate was studied by Mueller, Fickas and Cox.<sup>411</sup> In general, the published work along this

408 Elman, R. Oral Use of the Amino-Acids of Hydrolyzed Casein (Amigen) in Surgical Patients, *Am J Digest Dis* **10** 48, 1943.

409 Brunschwig, A., Clark, D. E., and Corbin, N. Postoperative Nitrogen Loss and Studies on Parenteral Nitrogen Nutrition by Means of Casein Digest, *Ann Surg* **115**:1091, 1942.

410 Shohl, A. T. Nitrogen Storage Following Intravenous and Oral Administration of Casein Hydrolysate to Infants with Acute Gastro-Intestinal Disturbance, *J Clin Investigation* **22** 257, 1943.

411 Mueller, A. J., Fickas, D., and Cox, W. M., Jr. The Minimum Maintenance Requirement of an Enzymic Casein Hydrolysate, *Bull Johns Hopkins Hosp* **72** 110, 1943.

line has indicated that the adult maintenance requirement of protein is between 0.5 and 0.7 Gm per kilogram of body weight. The authors' experiments were carried out on 4 normal, active, healthy men. The studies of nitrogen balance on these subjects showed that the minimum requirement of an enzymic casein hydrolysate for maintenance is between 0.4 and 0.7 Gm per kilogram of body weight, which indicates its approximate equivalence with intact protein for maintenance. Larger quantities of amino acids are obviously required in the face of additional needs for protein, such as are encountered in various medical and surgical conditions. To badly depleted patients Landesman and Weinstein<sup>412</sup> administered as much as 50 to 100 Gm daily by the intravenous route, with added sodium chloride, vitamins and dextrose in sufficient amounts to bring the caloric intake to between 1,200 and 2,000 calories. Such solutions were administered slowly, 2 to 4 cc per minute, and the only reaction causing concern was the occasional development of phlebitis.

That the solutions may be administered at a much greater rate of speed without untoward results is indicated in a report of Gardner and Trent.<sup>413</sup> These authors gave a liter of 3 per cent amino acid solution intravenously in an average injection time of twenty minutes. Two such injections were given daily to adults and included dextrose, vitamins and sodium chloride in addition to the amino acids.

*Allergy*—The permeability of the gastrointestinal mucosa to allergens is worthy of critical and intensive study. One such study has been made by Hartley,<sup>414</sup> who tested the permeability of the gastrointestinal mucosa of guinea pigs to crystalline egg albumin. All of 21 animals given a single feeding of crystalline egg albumin acquired circulating antibodies to approximately the same average titer as after parenteral injection of the same material. An important percentage of the animals showed signs of anaphylaxis after subsequent feedings of the antibodies. Curiously, the incidence of anaphylactic shock was higher in scorbutic animals than in those fed supplements of vitamin C. The possibility that ingested egg albumin might be localized by the antibodies in the gastrointestinal mucosa, and thus prevented from reaching the general antibody-forming organs, is discussed.

Alimentary idiosyncrasies may lead to any one of the different manifestations of the allergic reaction. Hanhart<sup>415</sup> has made a thorough study of familial histories in selected cases. He cites the example of a family in which all members for three generations reacted with violent vomiting to a single, but different, article of food. On the other hand, exclusive alimentary idiosyncrasies limited to one food may be encountered in various generations of a family without giving rise to definite types of reactions. The symptoms caused by alimentary idiosyncrasy, he believes, are observed in the alimentary tract (enteral allergy), usually as secretory or motor disturbances. Genuine pathologic change in the tissues, such as ulceration, is rarely found in cases of enteral allergy.

That allergic disorders may simulate acute abdominal conditions is illustrated by Derbes and Bruno,<sup>416</sup> who describe attacks of serious abdominal pain with gen-

412 Landesman, R. L., and Weinstein, V. A. Intravenous Use of Amino Acids for Nutritional Purposes in the Surgical Patients, *Surg., Gynec & Obst.* **75** 300, 1942.

413 Gardner, C. E., Jr., and Trent, J. C. Intravenous Amino Acid Administration in Surgical Patients, Using an Enzymatic Casein Digest, *Surg., Gynec & Obst.* **75** 657, 1942.

414 Hartley, G., Jr. The Permeability of the Gastrointestinal Mucosa of Guinea Pigs to Crystalline Egg Albumin, *J. Immunol.* **43** 297, 1942.

415 Hanhart, E. Constitutional Aspects of Alimentary Idiosyncrasy, *Gastroenterologia* **66** 121, 1941.

416 Derbes, V. J., and Bruno, F. E. Serum Sickness Simulating Acute Abdominal Disorders, *Surgery* **13** 450, 1943.

eralized abdominal rigidity and fever following injections of antitoxin. In 1 instance it was not until twelve hours later that an urticarial rash associated with severe itching appeared and clarified the diagnosis.

The association of gastrointestinal allergy with the celiac syndrome has been studied by McKhann and his associates.<sup>417</sup> These authors have noted in recent studies that there may be an associated gastrointestinal allergy in certain cases of celiac disease. Whether the allergic disturbances are secondary to changes in absorption dependent on the celiac syndrome or whether the sensitization to food precedes and is responsible for the symptoms of celiac disease is not clear. The added observation that absorption from the gastrointestinal tract of a fat-soluble substance (vitamin A) may be impaired under conditions known to be due to allergy but in which gastrointestinal symptoms are minimal suggests that degrees of impairment of absorption may occur on an allergic basis and that gastrointestinal allergy may bear a causal relationship to the celiac syndrome.

One of the dangers of dietary limitation based on allergic disturbances is brought out in a report by Reed and his associates.<sup>418</sup> A case is reported in detail of a patient with a history of severe, acquired food allergy beginning at the age of 32. Dietary eliminations led to the subsidence of all symptoms and to fairly good health for nine years, at the end of which time an extreme nutritional enteritis was found in association with deficiency of vitamins, especially of vitamin B<sub>2</sub>.

*Miscellaneous Gastrointestinal Conditions*—Because of its rarity, instances of intestinal lipodystrophy (Whipple's disease) are worthy of mention. Two cases are reported by Pearse<sup>419</sup> and by Apperly and Copley.<sup>420</sup> The disease is characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. The majority of patients complain of early postprandial discomfort and gaseous distention and have a history of polyarthritis. Later there is diarrhea or steatorrhea, often with blood, with severe wasting and loss of weight. Roentgenograms of the gastrointestinal tract are not diagnostic. At autopsy the intestinal mucosa is seen to be largely replaced by "foam" cells, with added gross enlargement of the mesenteric lymph nodes by similar cellular infiltration. There is no interference with fat splitting, as determined by studies of the stools. Pearse presents data which suggest that the abnormal digestion of fat present in the disease is due to a fault in bile salt metabolism. This view was strengthened by the clinical response of his patient to administration of bile salts.

Abdominal emergencies secondary to vascular disease within the peritoneal cavity frequently offer diagnostic difficulties. A review of the literature on mesenteric vascular occlusion is therefore of interest. This is presented by Giamarino and Jaffe,<sup>421</sup> who offer a classification based on arterial and venous lesions, the former being due to embolism or thrombosis and the latter almost always due to thrombosis, usually associated with infection in the abdominal organs which are tributary to the portal vein. The article gives no new information, but presents the material in an orderly and sequential manner.

417 McKhann, C. F., Spector, S., and Meserve, E. R. The Association of Gastrointestinal Allergy with the Celiac Syndrome, *J. Pediatr.* **22** 362, 1943.

418 Reed, A. C., Carr, J. L., and Rochex, F. Multiple Deficiency Disease with Allergy and Nutritional Enteritis, *Am. J. Trop. Med.* **23** 333, 1943.

419 Pearse, H. E. Whipple's Disease, or Intestinal Lipodystrophy, *Surgery* **11** 906, 1942.

420 Apperly, F. L., and Copley, E. L. Whipple's Disease (Lipophagia Granulomatosis), *Gastroenterology* **1** 461, 1943.

421 Giamarino, H. J., and Jaffe, S. A. Mesenteric Vascular Occlusion. Review of the Literature and General Principles. Report of a Case with Operation and Recovery, *Arch. Surg.* **45** 647 (Oct.) 1942.

Unusual vascular diseases within the abdomen are discussed by Kimball and his associates<sup>422</sup> Forty cases, including instances of aneurysm of the abdominal aorta (atherosclerotic, dissecting and syphilitic), aneurysm of the splenic artery and occlusion of the aorta, the superior and inferior mesenteric arteries, the splenic and left gastric arteries, the inferior vena cava and the iliac, portal and splenic veins, are of extreme interest Periarteritis nodosa and malignant hypertension are also discussed All of the patients presented symptoms and signs pointing to intra-abdominal disease and for this reason are of particular interest to the clinician

A rare case of severe gastrointestinal hemorrhage is that reported by Gordon-Taylor<sup>423</sup> After several sharp attacks of hematemesis, his patient was operated on with a preoperative diagnosis of perforated peptic ulcer At operation the liver, gallbladder and pylorus were found to be bound together in a pulsating mass An aneurysm in the hepatic arterial system was suspected Autopsy revealed such an aneurysm, at the junction of the cystic artery and the bifurcation of the hepatic artery

Therapeutic damage to the lower part of the intestinal tract is well recognized as caused by various measures, the most important of which is irradiation of the uterus and adnexa An important contribution to this subject is provided by Aldridge,<sup>424</sup> who studied the end-results of irradiation in 189 cases of cancer of the corpus and cervix of the uterus In 16.9 per cent of the entire number, or 1 of every 6, some type of proved injury to the intestine developed This was more frequently encountered after irradiation for cancer of the cervix than after that for cancer of the body of the uterus Wigby<sup>425</sup> offers adequate confirmation of these figures in his report on 77 patients given radiation treatment for cancer of the cervix Fifty-five per cent of this series had intestinal reactions varying from slight diarrhea to formation of stricture The reaction was severe enough in 6 cases to demand colostomy The description of an autopsy is included in his article, in which the evidence suggested that fibrosis sufficient to obstruct the ureters may occur as a result of radiation treatment In patients suffering from second and third degree reactions occasional bleeding from the rectum may never entirely disappear Svien and Dixon<sup>426</sup> report an enterovaginal fistula resulting from heavy intravaginal irradiation by radium

Although not commonly encountered, serious rectal irritation may possibly occur after the rectal administration of tribromoethanol (Miltrex) Maloney<sup>427</sup> investigated the results of the rectal administration of solution of tribromoethanol (in amylene hydrate) in rabbits and noted that delayed death of these animals was caused by rectal inflammation, ulceration and sometimes perforation

New or unusual diagnostic procedures are worthy of brief comment, if for no other reason than to excite interest in the value of any given maneuver Good-

422 Kimball, S., Lipsitz, M. H., and Terplan, K. Unusual Vascular Diseases Within the Abdomen, *Am J Digest Dis* 10 30, 1943

423 Gordon-Taylor, G. A Rare Case of Severe Gastrointestinal Hemorrhage, with a Note on Aneurysm of the Hepatic Artery, *Brit M J* 1 504, 1943

424 Aldridge, A. H. Intestinal Injuries Resulting from Irradiation Treatment of Uterine Carcinoma, *Am J Obst & Gynec* 44 833, 1942

425 Wigby, P. E. Postirradiation Stricture of Rectum and Sigmoid Following Treatment for Cervical Cancer, *Am J Roentgenol* 49 307, 1943

426 Svien, H. J., and Dixon, C. F. Entero-Vaginal Fistula. Report of Case, *Proc Staff Meet, Mayo Clin* 18 185, 1943

427 Maloney, A. H. Visceral Lesions Associated with Tribromethanol Administered Rectally, *J Pharmacol & Exper Therap* 75 247, 1942

man<sup>428</sup> presents a preliminary report on an improved method of measuring the potential difference across the human gastric membrane and its clinical significance. The apparatus used for the determination of the potential is fairly elaborate, and in the method the electrode system makes no direct contact with the skin or stomach. A standard test was evolved, using the potential difference response to milk as the central control measurement. While no conclusive deductions were reached, the method appears useful, to the author's mind, in differentiating gastric ulcers from other gastric lesions, particularly early lesions. There can be little doubt that any measure calculated to increase the possibility of early diagnosis of gastric cancer is worthy of consideration, but one must be rather skeptical that such a method would prove superior to careful roentgenography and gastroscopy in suspected cases.

Yodice<sup>429</sup> describes a maneuver which serves to establish the differential diagnosis between muscular contraction from peritoneal reactions and that due to other causes. The patient is placed in the dorsal decubital position, with the thighs abducted and flexed to 90 degrees. The index and middle fingers are introduced into the rectum when with the left hand the abdomen is palpated at the site of the muscular contraction. If at the moment the anal sphincter is dilated the muscular contraction of the abdomen does not disappear, it may be concluded that the rigidity is due to peritoneal irritation. If the muscular spasm disappears with this maneuver, the author believes that the contraction is due to pain of a colicky type, for which an emergency surgical procedure is not required. He believes that it helps to establish a differential diagnosis in cases of severe voluntary spasm, "phantom" tumor and the like.

A possible means of learning peritoneoscopy without gaining experience on living subjects is suggested by Chaffee,<sup>430</sup> who performed this maneuver on 100 bodies within an average time of eight hours after death. Adequate observations were possible and revealed the type of information to be gained as well as the limitations of peritoneoscopy. The author's suggestion that such a procedure be utilized as a means of acquiring facility in the use of the peritoneoscope seems reasonable. The results of the examinations made are of some interest, inasmuch as intra-abdominal pathologic conditions were correctly diagnosed 90 times.

Advances in roentgenologic technic and comments on all important contributions to the recent literature on this subject are beyond the scope of this article. A complete clinical and roentgenologic review for the year has been prepared by Feldman<sup>431</sup> with particular reference to diseases of the digestive tract, one hundred and eighty-three references are included. In addition to articles already cited in the preceding pages, two articles are chosen for comment. One by Johnstone<sup>432</sup> is of interest. He attempts to differentiate between a true pyloric stenosis and pyloric spasm by roentgenologic observation. With the patient in the supine position and the left side slightly raised, and with a kilovoltage slightly lower than that normally employed for examinations following barium sulfate meals, a shadow representing the thickness of the gastric wall along the greater curvature can be defined in all cases of hypertrophy. If the soft tissue shadows measure over 4 mm, hypertrophy

428 Goodman, E. N. Improved Method of Measuring the Potential Difference Across the Human Gastric Membranes and Its Clinical Significance. Preliminary Report, *Surg, Gynec & Obst* **75** 583, 1942.

429 Yodice, A. New Sign to Differentiate Abdominal Muscular Rigidity in Cases of Acute Abdominal Conditions from That of Other Causes, *Am J Surg* **57** 457, 1942.

430 Chaffee, J. S. Postmortem Peritoneoscopy. Means of Learning Peritoneoscopy, *Ann Surg* **116** 843, 1942.

431 Feldman, M. A Clinical Roentgenological Review of the Literature for 1942, Pertaining to the Digestive Tract, *Am J Digest Dis* **10** 161, 1943.

432 Johnstone, A. S. Radiological Sign of Pyloric Stenosis, *Brit J Radiol* **16** 169, 1943.

should be considered likely, if over 5 mm, it is certainly present. In the differentiation between pyloric stenosis and pyloric spasm, the author considers that the presence of a thick gastric wall is overwhelmingly in favor of true stenosis. If the issue is between duodenal ulcer and pyloric cancer causing obstruction, the thick gastric wall favors the benign lesion. Such observations are extremely important if confirmed by other investigators.

A point of medicolegal importance is that presented by Dillon.<sup>433</sup> The presence of air in the digestive tract of a newborn infant can serve as proof of extrauterine respiration and hence as proof that the infant was born alive. The roentgen examination of a stillborn fetus at any time in its uterine life never reveals any traces of air in the digestive tract. Correctly made roentgenograms of dead fetuses that had been breathing, even for a very short time, always disclose the presence of air in the stomach or intestine and constitute evidence that the author thinks is incontrovertible as a test of extrauterine life. If this is true, it is of particular importance because the roentgenogram will have the value of a permanent document.

*Specific Infections and Chemotherapy*—The increasing incidence of bacillary dysentery and the importance of this specific infection is becoming rapidly apparent. The significance of this disease is apparent when one considers the aggregation of great numbers of men in military centers and in various communities. Silverman and Friedrichs<sup>434</sup> indicate the wide distribution in this country and suggest that it has become endemic in many states in the union, northern as well as southern. Possible complications, such as arthritis and myocarditis, are discussed in detail.

The wartime diarrheas are considered in full by Manson-Bahr,<sup>435</sup> who gives a detailed description of the various forms of bacterial dysentery and amebic dysentery, with notes on incidence, epidemic infestations and treatment, based on his wide experience in the tropics.

A carefully prepared study of a rural epidemic of Shiga dysentery is given by Caudill and his associates,<sup>436</sup> with a mortality rate of 10.3 per cent. This report of a small epidemic is presented in such a way as to illustrate the modes of contact and spread and the preventive measures indicated.

The persistence of dysentery infection and the development of chronic dysentery due to Shiga and Flexner infection in the northern part of the world is reported by Neyman<sup>437</sup> on the basis of careful studies of 751 patients. He stresses the necessity for careful bacteriologic examination of feces, and in discussing the transition from acute dysentery to the chronic form he lists the nature and course of the acute process, the patient's constitution and any chronic gastrointestinal disease preceding the acute dysentery as factors concerned in such transition.

The experience with infectious diarrhea in an Australian hospital in the Middle East is described by Hone and his associates.<sup>438</sup> Some 300 patients were seen, and although *Shigella* was encountered in only 13 cases and the disease was relatively mild with no fatalities, the average stay in the hospital was one month. Such a precautionary measure was taken primarily to detect carriers, if possible, and to provide complete convalescence.

433 Dillon, J. G. The Respiratory Function of the Digestive Tract as the Basis of Roentgenographic Life Test, *Am J Roentgenol* **48** 613, 1942.

434 Silverman, D. N., and Friedrichs, A. V. The Increasing Incidence and Complications of Chronic Bacillary Dysentery, *New Orleans M & S J* **95** 401, 1943.

435 Manson-Bahr, P. H. Dysentery and Diarrhea in Wartime, *Brit M J* **2** 346, 1942.

436 Caudill, F. W., Teague, R. E., and Duncan, J. T. A Rural Shiga Dysentery Epidemic, *J A M A* **119** 1402 (Aug 22) 1942.

437 Neyman, M. A. Clinical Aspects of Chronic Dysentery, *Sovet vrach zhur* **4** 266, 1941.

438 Hone, F. R., Keogh, E. V., and Andrew, R. Bacillary Dysentery in Australian Hospital in the Middle East, *M J Australia* **1** 631, 1942.

The nature of the intestinal lesion in bacillary dysentery in its earliest stages was studied by Penner and Bernheim<sup>439</sup> Following the intravenous administration of Shiga toxin, the authors noted general changes in the blood and local lesions in the bowel There were rapid development of hemoconcentration and great diminution in blood volume (as much as 30 per cent), with an accompanying circulatory state as a result of which there occurred a compensatory vasoconstriction in the duodenum of the dog and the cecum of the rabbit The toxin had no direct effect on the intestinal mucosa when brought into contact therewith, but its absorption through the mucosa led to the appearance of a lesion in the duodenum of the dog which the authors believe was the end result of a prolonged and pronounced homeostatic vasoconstriction

Brulé<sup>440</sup> observed disturbances in the sodium and potassium metabolism in severe bacillary dysentery and noted that the ratios of sodium to chlorine and of sodium to potassium in the urine are considerably reduced during the acute stages of the disease He was unable to determine why in certain cases chlorine appears to be eliminated in the urine in combination with potassium but not with sodium This phenomenon is observed in patients with extreme loss of muscular power Brulé assumes as a working hypothesis that in certain cachexias potassium is no longer fixed normally in the tissues and muscles and thus is excreted in excess in the urine, whereas the amount of sodium diminishes

A certain measure of the seriousness of the disease, or of any acute or chronic gastroenteritis, is reflected in the excretion of creatine in the urine, large amounts being found in patients showing extreme wasting, as shown by Schneider<sup>441</sup>

A complete résumé of the bacteriologic, epidemiologic, immunologic and chemotherapeutic aspects of bacillary dysentery is to be found in a pair of articles by Neter<sup>442</sup> He discusses infections by the Shiga, Flexner, Sonne, Schmitz and Newcastle varieties of the dysentery bacillus, with particular attention to stool culture, bacteriophage and serologic study He gives the mortality of the disease in this country as about 5 per cent The carrier problem is discussed from the point of view of diagnosis and treatment He agrees with other authors in the belief that chemotherapy seems to be preferable to serum therapy, a conclusion that by now is rather generally accepted The value of bacteriophage therapy is discussed, but largely on the basis of reports from the literature

By now it is well established that at least as far as certain strains are concerned the use of sulfonamide compounds is of real value in the treatment of the various types of bacillary dysentery That some strains of *Shigella* are more resistant to sulfonamide compounds than others is indicated in a report by Cooper and Keller,<sup>443</sup> who point out individual differences, for example, in the reaction to sulfapyrazine and sulfacetamide, on the basis of *in vitro* experiments

A well observed and well controlled epidemic of Sonne dysentery is reported by Yannet and his associates<sup>444</sup> Of the 44 patients with clinical dysentery, 17 were

439 Penner, A., and Bernheim, A. I. Studies in the Pathogenesis of Experimental Dysentery Intoxication, *J. Exper. Med.* **76** 271, 1942

440 Brulé. Disturbances in the Sodium and Potassium Metabolism in Severe Bacillary Dysenteries, *Bull. et mem. Soc. med. d. hôp. de Paris* **56** 561, 1940

441 Schneider, E. Disturbance in the Chemistry of the Skeletal Muscle in Chronic Gastroenteritis, *Zentralbl. f. inn. Med.* **60** 641, 1939

442 Neter, E. Bacteriological, Epidemiological, Immunological, and Chemotherapeutic Aspects of Bacillary Dysentery, *Gastroenterology* **1** 366 and 471, 1943

443 Cooper, M. L., and Keller, H. M. Sulfonamide Resistant *Shigella*, *Paradysenteriae* Flexner and *Shigella* Sonnei, *Proc. Soc. Exper. Biol. & Med.* **52** 92, 1943

444 Yannet, H., Leibovitz, A., and Deutsch, J. V. Sulfathiazole in Epidemic Sonne Dysentery, *J. A. M. A.* **120** 184 (Sept. 19) 1942



treated routinely, and 27 were given sulfathiazole in addition to routine treatment. The use of the drug was associated with a more rapid clinical recovery than was noted in the control group. However, in the group given sulfathiazole there was a significant prolongation of the time required before the rectal cultures became consistently negative, and there were relapses at varying intervals, a complication that did not occur in the control group. These authors conclude that the routine use of sulfathiazole in institutional epidemics is not desirable. In their cases positive cultures reappeared as late as three weeks after the cessation of treatment. They advise continued isolation for at least this period before negative stool cultures are considered significant.

The oral administration of sulfaguanidine daily for six days to monkeys<sup>445</sup> did not shorten the course of the disease produced in an isolated segment of the colon, presumably because of inadequate absorption of the drug. Hardy and his associates<sup>446</sup> studied the possible value of sulfaguanidine in the control of *Shigella dysenteriae* infection among the inmates of a hospital for persons with mental disease. After five days of treatment with the drug, the number of positive cultures and of infected persons was reduced by more than 50 per cent. After three days of treatment, those infected on admission to the study were almost free of infection. The dose of the drug was no less than 0.3 Gm. per kilogram of body weight daily for at least four days.

In the British Air Force personnel in the Middle East, 60 patients with mild bacillary dysentery were treated by Paulley<sup>447</sup> with saline laxatives, supplemented later with sulfaguanidine. The average stay in the hospital was fourteen and six-tenths days. For nearly 100 patients treated with sulfaguanidine or sulfapyridine alone the average period in bed was between four and five days. In an outbreak of severe Shiga dysentery, the average periods in bed were five and seven-tenths days for patients treated with sulfapyridine and eight days for patients treated with sulfaguanidine. He stresses the point, made by others, that administration of a sulfonamide compound should begin early in the acute phase, before the disease has spread or become chronic.

In a small selected garrison of the United States Army an undue prevalence of diarrhea was noted. An investigation by Cornell and his associates<sup>448</sup> showed that of 97 men 34 were found to have positive cultures for *Shigella paradysenteriae*, Flexner and "W." All were treated with sulfaguanidine (5 Gm. doses three times a day for three days). A second course was given to all whose cultures did not become negative after the first course. In the succeeding six months, five more surveys were made, no more positive cultures were found, and no more men were hospitalized from this unit because of diarrhea.

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445 Dack, G. M., and Hoskins, D. Effect of Oral Administration of Sulfanilylguanidine on Experimental Bacillary Dysentery in Isolated Loops of Colon of *Macaca Mulatta* and Its Effect When Introduced into the Loops, *J. Infect. Dis.* **72**: 11, 1943.

446 Hardy, A. V., Watt, J., and DeCapito, T. M. Studies of Acute Diarrheal Diseases. VI. New Procedures in Bacteriologic Diagnosis, *Pub. Health Rep.* **57**: 521, 1942. Watt, J., Hardy, A. V., and DeCapito, T. Studies of Acute Diarrheal Diseases. VII. Carriers of *Shigella Dysenteriae*, *ibid.* **57**: 524, 1942. Hardy, A. V., Watt, J., Peterson, J., and Schlosser, E. Studies of Acute Diarrheal Diseases. VIII. Sulfaguanidine in Control of *Shigella Dysenteriae* Infections, *ibid.* **57**: 529, 1942.

447 Paulley, J. W. Treatment of Bacillary Dysentery in the Middle East, *Lancet* **2**: 592, 1942.

448 Cornell, V. H., Watt, J., and Dammin, G. J. Sulfaguanidine in the Control of *Shigella Paradysenteriae* Infections in Troops, *Mil. Surgeon* **92**: 253, 1943.

Among 77 patients with bacillary dysentery selected for treatment in a general hospital in the Middle East by Brewer,<sup>449</sup> complete cure was obtained following the use of sulfaguanidine in 73 per cent of those with the acute form and in 55 per cent of those with the chronic form. Toxic symptoms occurred in only 9 of 51 patients with chronic dysentery, and there were none in those with acute dysentery. A report on bacillary dysentery in the Middle East by Fairley and Boyd<sup>450</sup> emphasizes the mildness of the dysentery that was encountered, even with Shiga infections. The general mortality rate has been low and the incidence much less than in the last war. Nevertheless, bacillary dysentery continues to cause great wastage in man power, especially as the period of hospitalization averages three or four weeks. Shiga dysentery accounted for about 10 per cent of all cases seen in the Middle East, and the most common organism was *Shigella Flexner* II.

One approach to the carrier problem was by careful sigmoidoscopic examinations. In certain cases of chronic Shiga dysentery, ulcers surrounded by normal-looking mucous membrane were found to contain Shiga bacilli six months after the original attack. From a military point of view, any person who had colicky pain followed by fever and diarrhea with loose stools containing flakes of mucus or mucus and blood was regarded at once as having bacillary dysentery and sent away without delay. Although most of the attacks were mild, death occurred in thirty-two hours in 1 instance at least. As already mentioned, serum treatment was disappointing. It relieved toxic features, but its benefit was rarely more than temporary. Sulfaguanidine was used in more than 500 cases, care being taken to combat dehydration. Except for a few instances of headache, nausea or rash, there were no toxic reactions to the drug. Sulfasuxidine and sulfamethazine were being used experimentally.

The effect of adequate treatment with sulfaguanidine, with comparison with control cases, is reported on by Oppen and Hale,<sup>451</sup> who describe two outbreaks of bacillary dysentery, one in 1939-1940 and the other in 1941-1942. In the first outbreak, no chemotherapy was employed, and in this group over half the patients maintained their infectivity for one month or longer. In the second outbreak, nearly 90 per cent of the patients involved had negative stool cultures for the dysentery bacillus for an average period of one hundred and five days following the administration of sulfaguanidine. The appearance of *Shigella* of Flexner in the stools of 4 patients after a first course of treatment indicated the necessity for continued laboratory examinations.

Poth and his collaborators<sup>452</sup> have continued their work on succinylsulfathiazole (sulfasuxidine), with particular attention to bacillary dysentery. Ten patients for whom the diagnosis was confirmed bacteriologically were given full doses of sulfasuxidine. The length of treatment varied from two to seventeen days. There were no failures and no deaths. The authors consider it especially significant that the response to this drug was immediate although the disease had been present for as long as three months before treatment had been undertaken. Smyth and

449 Brewer, A. E. The Use of Sulphaguanidine in Bacillary Dysentery, *Brit M J* 1 36, 1943.

450 Fairley, N. H., and Boyd, J. S. K. Bacillary Dysentery in the Middle East. Modern Chemotherapeutic Treatment, *Brit M J* 2 673, 1942.

451 Oppen, L., and Hale, V. Sulfaguanidine in Treatment of Dysentery (*Bacterium Flexneri*) Carriers, *J A M A* 119 1489 (Aug 29) 1942.

452 Poth, E. J., Chenoweth, B. M., Jr., and Knotts, F. L. A Preliminary Report on the Treatment of Bacillary Dysentery with Succinyl Sulfathiazole, *J Lab & Clin Med* 28 162, 1942.

his associates,<sup>453</sup> on the basis of control observations in an institution where there was an epidemic of bacillary dysentery, conclude that sulfasuxidine was as effective as sulfaguanidine as a therapeutic agent and preferable because of the lack of untoward reactions. They have observed that doses twice the amount ordinarily employed (0.25 Gm. per kilogram of body weight) could be administered safely, and they suggest that twice the amount of the original dose be given if fever and diarrhea are not controlled after three days of therapy with smaller doses.

The use of bacteriophage in the treatment of bacillary dysentery receives comment from various investigators. Compton,<sup>454</sup> like Russian observers, believes that bacteriophage therapy is effective and valuable. This conclusion is based on a statistical examination of mortality rates resulting from bacillary dysentery in Alexandria. A more recent Russian report, by Yemoleva,<sup>455</sup> records the favorable results associated with the use of small amounts of sulfapyridine during bacteriophage treatment. It is quite possible that the more recent intensive use of sulfonamide derivatives will eventually be adopted on the basis of reports like the preceding ones.

Commenting on experiences in two outbreaks of dysentery in army camps in Germany, Dotzer and Schuller<sup>456</sup> also comment on the value of bacteriophage therapy for persons infected by *Shigella* of Flexner. Rivanol proved effective in treatment of bacillus carriers. A possible point of importance was noted in the impression of these authors that resistance to the organisms was influenced by an adequate vitamin content of the food and that this factor was probably of great importance in a favorable outcome. This report is of interest as recording an excellent epidemiologic study in an army camp.

Gatewood,<sup>457</sup> in commenting on the treatment of intestinal disorders in military forces, discusses the various forms of therapy and stresses one point which is important, because of the variety of the drugs used in the treatment of various forms of disease to which soldiers may be exposed. He insists emphatically on the necessity for careful and accurate recording of all medication given, which record should always go with the patient when he is transferred from one hospital to another.

The prophylactic use of sulfaguanidine has been mentioned before but deserves comment. Scott<sup>458</sup> discusses the handling of an incipient epidemic of Sonne dysentery in a school for mentally defective children. After 2 cases had developed and segregation and other methods of treatment had failed, the prophylactic use of sulfaguanidine was tried, being given to all well children and personnel in the building. The epidemic was stopped abruptly. The dosage for each subject, adult or child, was 0.5 Gm. three times a day by mouth. No toxic signs were noted. Experimental evidence confirming the prophylactic value of sulfaguanidine therapy and possibly the use of other sulfonamide derivatives is available in several reports. Bloomfield and Lew,<sup>459</sup> in studying the problem of ulcerative colitis of rats, noted

453 Smyth, C. J., Finkelstein, M. B., Gould, S. E., Koppa, T. M., and Leeder, F. S. Acute Bacillary Dysentery (Flexner). Treatment with Sulfaguanidine and Succinylsulfathiazole, *J. A. M. A.* **121** 1325 (April 24) 1943.

454 Compton, A. Results of Bacteriophage Treatment of Bacillary Dysentery at Alexandria. A Statistical Retrospect, *Brit. M. J.* **1** 719, 1942.

455 Research in the U. S. S. R. Treatment of Dysentery, editorial, *Brit. M. J.* **2** 349, 1942.

456 Dotzer and Schuller. Experiences in Two Outbreaks of Dysentery in Camps, *Deut. Militararzt* **6** 95 and 160, 1941.

457 Gatewood, L. C. The Treatment of Intestinal Disorders in the Military Forces, *Am. J. Digest. Dis.* **9** 359, 1942.

458 Scott, J. C. Prophylactic Use of Sulfaguanidine, *J. A. M. A.* **122** 588 (June 26) 1943.

459 Bloomfield, A. L., and Lew, W. Prevention of Infectious Ulcerative Colitis in Young of Rats by Chemotherapy of Mother, *Am. J. M. Sc.* **205** 383, 1943.

that the young of rats which received 0.5 per cent sulfaguanidine in their food during pregnancy and lactation only occasionally acquired the disease, whereas three fourths of the young of untreated mothers acquired it. The young of treated mothers raised in the same cages with the young of untreated mothers had cecitis much more frequently than if segregated, but a high degree of resistance is still demonstrable. In a maternity hospital in Edinburgh, Scotland, Henderson<sup>460</sup> noted the incidence of gastroenteritis in a total of 102 infants over a three year period. Fifty-two infants were mature, and 52 were premature. In the latter group, the incidence was very much higher. For 72 untreated patients in the years 1940 to 1942, the mortality rate was over 70 per cent. Of 30 patients treated in 1942 with sulfaguanidine, 90 per cent recovered, and this rate would have been even better had it not been for the fact that 19 of the 30 were premature infants.

The possible value of calcium therapy for bacillary dysentery was studied with particular reference to children and infants by Block and Tarnowski.<sup>461</sup> Apparently complete healing and a reduction in mortality from 6 to 2 per cent were observed in the patients receiving calcium (gluconic acid salts) parenterally and orally. The effects of calcium salts in reducing abnormal motor activity are well known, but it is dubious whether such a therapeutic procedure offers anything comparable to the results to be obtained by the use of one of the sulfonamide compounds.

In 1941, Tudor found sulfathiazole and sulfaguanidine satisfactory in the treatment of infantile diarrhea, with sulfathiazole apparently more effective in the parenteral types (secondary to infection elsewhere, usually in the upper respiratory tract). In the present report<sup>462</sup> the effects of sulfadiazine are compared with results obtained by one of its isomers, sulfapyrazine. Both drugs seemed to be equally effective.

Forty-six children suffering with infectious diarrhea were treated by the use of sulfathiazole. Rubens and his associates<sup>463</sup> found that a diminution of stay in the hospital and more rapid relief of symptoms were obtained in those instances in which stool cultures were positive for *Salmonella* organisms.

Another example of the prophylactic value of sulfaguanidine therapy is found in a report by Lucchesi and Gildersleeve.<sup>464</sup> Forty-five patients intimately exposed in an outbreak of bacillary dysentery were given a prophylactic dose of the drug. None of these patients contracted the disease.

The effect of therapy with sulfonamide compounds on the bacterial flora of the bowel has been studied by various investigators and has been previously reported. Coliform organisms are usually affected and are diminished in number or disappear from the intestinal flora, only to be replaced by other organisms of the gram-negative type. As a complete intestinal antiseptic, therefore, the drugs still leave much to be desired, a point already noted by Poth and many others and demonstrated, for example, in a recent report by Vieta and Stevenson<sup>465</sup> in relation to sulfa-

460 Henderson, J. L. Sulfaguanidine in Neonatal Epidemic Gastro-Enteritis, *Brit. M. J.* **1** 410, 1943.

461 Block, L. H., and Tarnowski, A. Calcium Therapy in Bacillary Dysentery with Particular Reference to Children and Infants, *Rev. Gastroenterol.* **9** 300, 1942.

462 Tudor, R. B. Chemotherapy of Infantile Diarrhea. A Comparison of Sulfadiazine and Sulfapyrazine, *J. Pediat.* **22** 652, 1943.

463 Rubens, E., Kaplan, M., Borovsky, M. P., and Blatt, M. L. The Effect of Sulfathiazole in the Treatment of Dysentery in Children, *J. Pediat.* **22** 70, 1943.

464 Lucchesi, P. F., and Gildersleeve, N. Prophylactic Use of Sulfanilguanidine in a Dysentery Outbreak, *J. Pediat.* **22** 319, 1943.

465 Vieta, J. O., and Stevenson, E. S. The Use of Sulfaguanidine as an Intestinal Antiseptic, *Am. J. Surg.* **58** 377, 1942.

guanidine The rather striking effect on coliform organisms following the use of succinylsulfathiazole, with particular reference to colonic surgery, has been stressed by Poth and Knotts <sup>466</sup>

A report corroborating previous studies as to the favorable effect of sodium sulfanilylsulfanilate in cases of lymphogranuloma venereum is presented by Levy and his colleagues <sup>467</sup> One hundred and eighteen patients were treated, with disappearance of local symptoms, regeneration of mucosa and a diminution of edema and infiltration around the rectal strictures Prolonged administration is necessary

A large number of papers are concerned with the intraperitoneal administration of one or another of the sulfonamide derivatives Their use in this fashion is now practiced widely in the treatment and prevention of infection, particularly of the peritoneal cavity Depending on the derivative used, the absorption from the peritoneal cavity varies Pearl and Rickles <sup>468</sup> found in rats that sulfathiazole was more rapidly absorbed from an infected peritoneum than from a normal one Tashiro and his associates <sup>469</sup> noted in rabbits that a maximum absorption of sulfanilamide crystals took place in four hours but that an extremely high concentration was maintained intraperitoneally until the maximum blood concentration was reached In a patient with pneumococcic peritonitis, sulfathiazole administered orally and parenterally was found by Slobody and his associates <sup>470</sup> to produce a good response The patient responded well clinically to the oral administration of the drug, but the peritoneal fluid became sterile only after intraperitoneal instillation The possible dangers from intraperitoneal sulfanilamide therapy should include the occurrence of hepatic damage Hudson and Smith <sup>471</sup> report 1 patient with evidence of jaundice in a large group of patients given such treatment, although Jackson and Collier <sup>472</sup> previously had noted the frequency with which jaundice was associated with intraperitoneal injection of sulfanilamide in conjunction with oral administration of this drug The actual distribution of the drug in the peritoneal cavity and the coexistence of minor degrees of hepatic damage undoubtedly may act as conditioning factors in this complication

Poth and Bravo Fernandez, <sup>473</sup> on the basis of careful experiments on dogs, have demonstrated the effectiveness of intraperitoneal use of sulfathiazole and suggest that a suspension of the drug may be more suitable than the dry powder for intraperitoneal administration and that repeated injections may be advisable in cases of generalized peritonitis Ambrose and his associates <sup>474</sup> are in accord with this view and believe that associated oral therapy is advisable

466 Poth, E J, and Knotts, F L Clinical Use of Succinylsulfathiazole, Arch Surg **44** 208 (Feb) 1942

467 Levy, J G, Holder, E G, and Bullowa, J G M Stricture of the Rectum Due to Lymphogranuloma Venereum Symptoms and Treatment with Sodium Sulfanilyl Sulfanilate, Am J Digest Dis **9** 237, 1942

468 Pearl, M J, and Rickles, J A Local Implantation of Sulfathiazole as Therapeutic and Prophylactic Measure in Peritonitis Experimental Study, West J Surg **50** 99, 1942

469 Tashiro, K, Pratt, O B, Kobayashi, N, and Kawaichi, G K The Local Implantation of Sulfanilamide in the Peritoneal Cavity and Its Clinical Application in Peritonitis, Surgery **11** 671, 1942

470 Slobody, L B, Rook, G, and Dragutsky, D Diffusion of Sulfathiazole into and from the Peritoneum, J Pediat **20** 182, 1942

471 Hudson, R V, and Smith, R Intraperitoneal Sulfanilamide Its Prophylactic and Therapeutic Value, Lancet **1** 437, 1942

472 Jackson, H C, and Collier, F A Use of Sulfanilamide in Peritoneum Experimental and Clinical Observations, J A M A **118** 194 (Jan 17) 1942

473 Poth, E J, and Bravo Fernandez, E Experimental Studies of the Value of Sulfathiazole in Peritonitis, Surgery **13** 847, 1943

474 Ambrose, A M, Griswold, R A, and Hamilton, J E Absorption of Sulfadiazine After Oral and Intraperitoneal Administration in Dogs and After Intraperitoneal and Local Administration in Man, Am J M Sc **205** 376, 1943

Walter and Cole,<sup>475</sup> on the basis of observations on a large number of dogs, conclude that sulfadiazine is superior to sulfanilamide in the prevention of infection of wounds following administration by the intraperitoneal route. Their studies revealed a much more persistent blood level with sulfadiazine than with sulfanilamide. In cases of traumatic peritonitis, Gilchrist and his associates<sup>476</sup> believe that intravenous administration of sodium sulfathiazole is more advantageous. They state that fifteen minutes after its injection the effective sulfathiazole level in the peritoneum will approach that in the blood. Therapeutic concentration in the peritoneal fluid, they say, will be maintained for four to six hours.

The necessity for care in the distribution of intraperitoneally applied sulfonamide compounds is stressed by Crutcher and his associates<sup>477</sup>. In experiments on dogs the effect of sulfanilamide, sulfathiazole and sulfadiazine on the peritoneum was noted. All the drugs may produce adhesions within the peritoneal cavity under certain conditions and are apt to become walled off as a foreign body and be absorbed slowly. Sulfadiazine was absorbed more slowly than the other two drugs from the peritoneal cavity and produced greater local reactions. The authors advocate the administration of the drugs in a suspension of sterile water or saline solution. Laird and Stavern,<sup>478</sup> on the basis of animal experiments, have found that sodium sulfathiazole should not be used intraperitoneally because of severe local reactions.

The possible beneficial effects of vaccines and irradiation in the prevention or treatment of peritonitis following operation is discussed by Dixon and his associates<sup>479</sup> and by Rigos<sup>480</sup> respectively. Such methods are worthy of study, but, in view of the favorable results attendant on therapy with sulfonamide compounds, they presumably have less to offer.

Food poisoning is frequently due to staphylococci and fecal streptococci. In studying the response of intestinal muscle of rabbits to the enterotoxin extracted from strains of staphylococci cultured from food known to have produced attacks of food poisoning, Richmond and Reed and their associates Shaughnessy and Michael<sup>481</sup> found that the tonicity of smooth muscle was predominantly increased. This increased tonicity may be comparable to clinical enterospasm, to which much of the gastrointestinal pain experienced in food poisoning may be attributed. Their experiments confirm earlier ones showing that the enterotoxin need not be absorbed through the intestinal mucosa to produce its effect on the smooth muscle of the gastrointestinal tract. The effect is probably that of a nonspecific irritant. *Streptococcus faecalis* has been shown to possess great resistance to sulfonamide

475 Walter, LeR., and Cole, W. H. The Intraperitoneal Administration of Sulfadiazine, with Special Reference to a Comparative Study with Sulfanilamide, *Surg., Gynec. & Obst.* **76** 524, 1943.

476 Gilchrist, R. K., Straus, F. H., Hanselman, R., Draa, C. C., Lawton, S. E., and Freeland, M. Traumatic Peritonitis. Choice of Routes for the Administration of Sulfonamides, *Surg., Gynec. & Obst.* **76** 689, 1943.

477 Crutcher, R. R., Daniel, R. A., Jr., and Billings, F. T. The Effect of Sulfanilamide, Sulfathiazole and Sulfadiazine upon the Peritoneum, *Ann. Surg.* **117** 677, 1943.

478 Laird, G. J., and Stavern, H. Intraperitoneal Use of the Sulfonamides, *California & West Med.* **56** 293, 1942.

479 Dixon, C. F., Barger, J. A., and Tennison, W. J. Intraperitoneal Injection of Vaccine in Prevention of Postoperative Peritonitis, *Arch. Surg.* **45** 507 (Oct.) 1942.

480 Rigos, F. J. Roentgenologic Irradiation in Acute Peritonitis and Its Effect on the Cells of Normal Peritoneal Fluid in Guinea Pigs, *Radiology* **39** 681, 1942.

481 Richmond, J. J., Reed, C. I., Shaughnessy, H. J., and Michael, V. The Effect of *Staphylococcus Enterotoxin* on Isolated Rabbit Gut Segments, *J. Bact.* **44** 201, 1942.

compounds and to penicillin. In vitro experiments by Rodaniche and Palmer<sup>482</sup> showed that tyrothricin, a substance isolated by Dubos (1939), is highly bacteriostatic and bactericidal against fecal streptococci, but with marked variations in different strains. The oral administration of tyrothricin to mice was shown to produce inhibition of the growth of streptococci in the intestinal tract. This was most readily demonstrated when sulfasuxidine was administered together with the tyrothricin.

Like other observers, Watt and Peterson<sup>483</sup> were able to demonstrate no therapeutic effect from sulfaguanidine in the treatment of patients with proved typhoid. Little effect in vitro was found on typhoid organisms by Cooper and Keller,<sup>484</sup> using sulfathiazole and sulfaguanidine. Hesser<sup>485</sup> suggests, on the basis of in vitro experiments, that sodium phentetiothaleim in neutral or bile solution is bactericidal for *Eberthella typhi* in higher dilutions than is sodium iodophthaleim. Brownlee and Tonkin,<sup>486</sup> also on the basis of in vitro experiments, believe that sulfamylbenzamide has definite deleterious effects against the typhoid bacillus. Caile<sup>487</sup> claims successful results for the treatment of paratyphoid carriers with sodium iodophthaleim. The article is not conclusive, but the method certainly warrants careful study. Mice infected with strains of *Eberthella typhi* in the VI phase were almost completely protected by the intravenous use of specific bacteriophage, as indicated in a report by Ward.<sup>488</sup> It is to be earnestly hoped that some form of bacteriophage or chemotherapy may at length be found effective in the treatment of patients with typhoid or of typhoid carriers.

Perforation of tuberculous ulcers of the intestinal tract is not particularly common. An impression of its frequency may be gained from an article by Lamberti,<sup>489</sup> who describes 9 cases observed in a series of 258 cases of intestinal lesions. On the basis of what seem to be careful clinical studies of 221 patients with pulmonary tuberculosis, Tchertkoff and Green<sup>490</sup> believe that a diagnosis of intestinal tuberculosis may be made in spite of the absence of any other clinical sign or symptom in cases of pulmonary tuberculosis in which there has been fever for more than two months. Such a conclusion is of extreme importance if borne out by subsequent clinical observations.

482 Rodaniche, E. C., and Palmer, W. L. The Action of Tyrothricin on Fecal Streptococci in Vitro and in Vivo, *J. Infect. Dis.* **72** 154, 1943.

483 Watt, J., and Peterson, J. S. Sulfaguanidine Noneffective in Treatment of Typhoid Fever and Typhoid Carriers, *Pub. Health Rep.* **57** 872, 1942.

484 Cooper, M. L., and Keller, H. M. Susceptibility of *Shigella Paradyseriae* to Sodium Sulfathiazole and Sulfaguanidine in Vitro with Some Information Regarding *Eberthella Typhosa*, *Salmonella Paratyphosa*, *Escherichia Coli*, *Salmonella Morgagni* and *Proteus*, *J. Pediat.* **22** 418, 1943.

485 Hesser, F. H. A Note on Some Experimental Results Suggesting the Use of Sodium Phentetiothaleim in the Treatment of Enteric Infections of Bacillary Origin, *North Carolina M. J.* **3** 359, 1942.

486 Brownlee, G., and Tonkin, I. M. Sulfamylbenzamide in the Chemotherapy of Bacillary Dysentery, *Trop. Dis. Bull.* **39** 35, 1942.

487 Caile, R. Treatment of Intestinal Carriers of the Enteric Group of Organisms, *Brit. M. J.* **1** 604, 1943.

488 Ward, W. E. Protective Action of VI Bacteriophage in *Eberthella Typhi* Infections in Mice, *J. Infect. Dis.* **72** 172, 1943.

489 Lamberti, C. E. Perforation of Tuberculous Ulcers of Intestine, *Ann. Cated. de pat. y clin. tuberc.* **3** 397, 1941.

490 Tchertkoff, I. G., and Green, H. Importance of Fever as Diagnostic Sign of Intestinal Involvement in Chronic Pulmonary Tuberculosis. Considerations on Pathogenesis, *Quart. Bull., Sea View Hosp.* **7** 230, 1942.



An unusual type of infection is reported by Thompson and his associates,<sup>491</sup> who describe a patient with lesions of blastomycosis only in the cecum. Complete extirpation of the cecum and the terminal portion of the ileum apparently produced a cure. The authors state that in this country the majority of cases of blastomycosis have been reported from the Chicago area.

*Gastrointestinal Problems Relating to the War*—The effect of the war on the incidence and variety of gastrointestinal symptoms is becoming increasingly obvious. Many of the articles already referred to have a direct bearing on the medical care of troops or personnel engaged in war activities. Civilians as well as persons in military service are affected by the pressure and strain of war conditions. Gastrointestinal disease among industrial workers ranks second only to respiratory disease as the greatest cause of absenteeism in industry. McGee and Greger<sup>492</sup> report that nearly 20 per cent of the time lost by the employees of a large powder company was due to gastrointestinal disease. Eighty per cent of the digestive disorders could be classified under the heading of gastrointestinal upset and colonic dysfunction. The incidence of gastrointestinal disease and the distribution of persons suffering from any of its phases are thus a cause of increasing concern in the armed services of all countries. Peptic ulcer, gastritis and specific infections of the bowel constitute the vast majority of organic ailments encountered in the alimentary tract, but an even larger number of indeterminate gastrointestinal complaints due to disturbances of function of digestion are presented and offer serious diagnostic difficulties, particularly because of their psychologic aspects.

All authorities agree that the diagnosis of ulcer precludes the performance of active duty and justifies exclusion or rejection, as the case may be, except in a small number of individual cases in which limited service for particular purposes is indicated.

Any of the factors responsible for the high incidence of dyspepsia with no demonstrable organic disease are obvious. Psychologic disturbances, including boredom from a protracted period of training, the disposition of men to areas where recreation of the type they are accustomed to is not to be had or where they suffer anxiety about their families and the irritation caused by their comparing their pay with the high wages of munitions workers, cannot be overlooked. An excellent discussion of the dyspeptic soldier and his disposal is to be found in an article by Hill,<sup>493</sup> who reports his experiences with British troops.

In the Swiss army<sup>494</sup> gastric tumors and recurrent gastroduodenal ulcers constitute cause for rejection from active service, as do the severe forms of anacid, atrophic gastritis resistant to treatment. Knapp,<sup>495</sup> in Switzerland, reports that it is impossible to render a final decision regarding fitness for service of persons with various gastric disorders until adequate exclusion of serious disease has been made by roentgenography—a conclusion about which there can be no controversy.

The importance of gastroscopy is stressed by Gill,<sup>496</sup> as well as by many American authors, and he analyzes the results of over 1,000 gastroscopic examinations.

491 Thompson, G. F., Sullivan, M. J., and Fox, P. F. Blastomycosis of the Cecum. Case Report, *Am J Surg* **57** 369, 1942.

492 McGee, L. C., and Greger, J. D. Gastrointestinal Disease Among Industrial Workers, *J A M A* **120** 1367 (Dec 26) 1942.

493 Hill, L. C. Dyspepsia in the Army, *Lancet* **1** 452, 1943.

494 Demole, M. Evaluation of Fitness of Gastric Patients for Military Service, *Helvet med acta* **8** 722, 1941.

495 Knapp, H. Experiences with Gastric Patients in Military Service, *Helvet med acta* **8** 727, 1941.

496 Gill, A. M. Evaluation of Gastroscopy. Analysis of One Thousand Examinations, *Lancet* **1** 333, 1943.

of persons in military service According to his studies, nearly half of 806 soldiers had gastritis, but this percentage is considered altogether too high by Edwards,<sup>497</sup> who found a much lower figure for the incidence of gastritis He cites 2 instances of serious gastritis in young sailors who had suffered great hardship on constant mine-sweeping patrols in the North Sea Such a finding is undoubtedly to be encountered in many instances among men engaged in work on small vessels in the North Atlantic, and may be a cause for serious disability

The relation of gastric disease to military service needs classification This is pointed out by Palmer,<sup>498</sup> who stresses particularly the fact that ulcerative gastritis may be associated with an ulcer-like distress or with massive hemorrhage or both Patients with this condition, for practical military purposes, should be included in the group with ulcers and should be treated accordingly

The actual incidence of gastritis capable of producing symptoms in the armed forces of the United States is indicated in reports by Gold<sup>499</sup> and McGlone<sup>500</sup> The groups studied are too small to be conclusive but indicate the potential importance of gastroscopic findings

Authorities agree that the majority of patients suffering from ulcer in the armed services on occasion had symptoms of ulcer prior to entering service Recent reports from certain fronts are beginning to suggest that the incidence of new ulcers in patients previously free from symptoms of ulcer may be increasing, but statistical data are not yet available Such a finding would not be surprising but would be of tremendous importance as indicating the causative influence of prolonged stress and strain In the American services, duodenal ulcer predominates by a tremendous percentage over gastric ulcer Reports by Chamberlin,<sup>501</sup> Logan and Bransford<sup>502</sup> and Flood<sup>503</sup> indicate that between 85 and 95 per cent of all patients with ulcer had duodenal lesions In the Surgeon General's report, quoted by Flood, the incidence of gastric ulcer in the United States Navy was 15 per cent, a figure identical to that reported in the Royal Navy by Wade<sup>504</sup>

Psychologic factors predisposing to ulcer are well recognized That these may be operative even in noncombat duty has already been emphasized and is again stressed by Dunn,<sup>505</sup> who states that the frequency of gastroduodenal disorders may be partly due to prolonged tension in men who have been mobilized for war but who have little opportunity for carrying off emotions in combatant activity Such a conception is borne out by Wade's statement that in his comparison of men on active service in the Royal Navy with reserves and "hostilities-only" personnel, the ratio of men with dyspepsia in the two groups was found to be 1 to 3.7

497 Edwards, H. C. Evaluation of Gastroscopy, *Lancet* **1** 474, 1943

498 Palmer, W. L. The Stomach and Military Service, *J. A. M. A.* **119** 1155 (Aug. 8) 1942

499 Gold, R. L. Gastroscopic Findings in Patients with Dyspepsia at an Army Hospital, *Gastroenterology* **1** 254, 1943

500 McGlone, F. B. Incidence of Gastritis in Soldiers and War Veterans, *Gastroenterology* **1** 258, 1943

501 Chamberlin, D. T. Peptic Ulcer and Irritable Colon in the Army, *Am. J. Digest. Dis.* **9** 245, 1942

502 Logan, V. W., and Bransford, P. W. Peptic Ulcer in the U. S. Navy, *Ann. Int. Med.* **18** 929, 1943

503 Flood, C. A. Peptic Ulcer at Fort George G. Meade, Md., *War Med.* **3** 160 (Feb.) 1943

504 Wade, H. J. Dyspepsia in the Royal Navy. A Study of 1003 Consecutive Cases, *Lancet* **2** 636, 1942

505 Dunn, W. H. Gastroduodenal Disorders. An Important Wartime Medical Problem, *War Med.* **2** 967 (Nov.) 1942

The incidence of perforation from ulcer has increased, as indicated by the figures presented by Riley<sup>506</sup>. In the Royal Victoria Infirmary in Newcastle, there were 200 perforations in 1939, 222 in 1940 and 251 in 1941. The probable cause for the increase in perforated peptic ulcers in London is ascribed by Stewart and Winsor<sup>507</sup> to increased anxiety and tension. Figures obtained from 1937 to 1940 from sixteen London hospitals showed a statistically significant increase in perforations during the first heavy air raids of the fall of 1940. Ninety-three per cent of the perforations were in men. An interesting fact in this report is found in the statement that the peak incidence for the entire four year period was in persons from 50 to 60 years of age. This figure is in sharp contrast to the peak incidence during the air raid period in 1940, when the largest number of persons affected were between the ages of 21 and 40.

One of the most interesting, as well as one of the most distressing, types of injury encountered in the present struggle is that known as immersion blast or hydraulic abdominal concussion. The outstanding feature of this condition is forceful compression of the abdominal or thoracic organs produced in partially or completely submerged persons. The explosion of a depth charge may give some manifestation in the air by blowing surface water up, but its chief effect is attained in the water within a radius of several hundred yards. Damage occurs particularly to the lungs and the walls of certain intestinal loops. It may be slight or severe, depending on the intensity and proximity of the blast waves. The rupture of intestinal vessels produces ecchymosis and hematoma in the wall of the affected loops and subsequent ileus. Perforation may occur, with resulting generalized peritonitis, abscess formation or intestinal gangrene. Damage to the stomach or intestinal tract depends, among other factors, on the presence of air in the viscus. Some protection can be obtained from kapok or from rubber coverings, such as are found in "Mae West" life-preservers. Observers seem to agree that operation should not be performed except for recent and rapidly diagnosed perforation or strangulation. In most instances treatment should be predominantly conservative and should be directed toward the prevention or treatment of shock. A complete consideration of the condition is to be found in a symposium<sup>508</sup> on immersion blast injuries by several contributors, which covers a discussion of the mechanism and pathologic features of the condition, the surgical aspects and the roentgenologic findings. Additional articles contributing importantly to the same subject, including the experimental reproduction of such injuries, are presented by various authors (Auster and Willard<sup>509</sup>, Friedell and Ecklung<sup>510</sup>, Greaves and others<sup>511</sup>, Pinnock and Wood<sup>512</sup>).

A most comprehensive article by Gordon-Taylor<sup>513</sup> on the abdominal surgery of "total war" includes the results of two and one-half years of war experiences

506 Riley, I. D. Perforated Peptic Ulcer in War-Time, *Lancet* **2**:485, 1942.

507 Stewart, D. N., and Winsor, D. M. deR. Incidence of Perforated Peptic Ulcer Effect of Heavy Air Raids, *Lancet* **1** 259, 1942.

508 Symposium on Immersion Blast Injuries, *U. S. Nav. M. Bull.* **41** 1, 1943.

509 Auster, L. S., and Willard, J. H. Hydraulic Abdominal Concussion. The Syndrome of Intra-Abdominal Underwater Blast Injury, *J. A. M. A.* **121** 995, (March 27) 1943.

510 Friedell, M. T., and Ecklung, A. M. Experimental Immersion Blast Injury. Preliminary Report, *U. S. Nav. M. Bull.* **41** 353, 1943.

511 Greaves, F. C., Draeger, R. H., Brines, O. A., Shaver, J. S., and Corey, E. L. Experimental Study of Underwater Concussion, *U. S. Nav. M. Bull.* **41** 339, 1943.

512 Pinnock, D. D., and Wood, P. Blast Injury to the Abdomen by Depth Charge, *Brit. M. J.* **1** 537, 1943.

513 Gordon-Taylor, G. The Abdominal Surgery of "Total War," *Brit. J. Surg.* **30** 89, 1942.

in England. This article covers abdominal injuries suffered during "total war" encountered both in military service and in civilian life. Six hundred cases are analyzed, and careful histories are given illustrating abdominal injuries in pregnancy and parturition, injuries from glass and bomb fragments and bone fragments, trauma due to nonpenetrating missiles and bayonet wounds. The value of therapy with sulfonamide compounds is naturally emphasized. The author states that despite the gravity of the wounds and the frequent association of multiple injuries, approximately 50 per cent of the patients with abdominal injury for which operation was possible survived. The percentage of recovery from injuries of the stomach, small intestine and rectum is much higher than that observed in the last war. The recovery rate from injury of the large bowel is about the same as in the preceding period. The frequency of acute dilatation of the stomach, in cases both of abdominal injury and of damage to other parts of the body, has been impressive. This phenomenon may occur as an immediate concomitant of the injury or may complicate the later history of a laparotomy undertaken to repair abdominal wounds.

The importance of antityphoid inoculation is dramatically presented in an article by Boyd<sup>514</sup> on the basis of observations among Italian prisoners taken in the Libyan campaign and of somewhat similar observations made on a large number of British prisoners kept in Axis concentration camps. The conclusion was reached that the relative immunity to typhoid enjoyed by the British troops in captivity was attributable to the use of a potent vaccine. Similar immunity was not enjoyed by the Axis forces, who had a high endemic rate and among whom an outbreak of considerable magnitude occurred despite inoculation with vaccine of Italian manufacture. In one concentration camp of 24,000 British prisoners, 12,000 cases of dysentery occurred because of almost impossible sanitary conditions. As far as could be learned, no case of typhoid was encountered in this large number of persons. Among Italian troops previously inoculated and captured in Libya, a major outbreak occurred in 1940. The newly captured men were inoculated with British vaccine, and from that time on the incidence of typhoid was low until the influx from the El Alamein battle started in 1942. Roughly 1,200 cases occurred among Italian prisoners between 1941 and 1943, inclusive. An unusual sequel of typhoid inoculation is recorded by Bowers and Shupe<sup>515</sup>. Immediately after each new increment of troops was inoculated against typhoid in one United States Army camp, the authors noted that there was an influx of patients with acute appendicitis. The time relationship between the inoculation and the development of acute appendicitis was so striking that they investigated the situation and concluded that acute appendicitis on the basis of luminal obstruction by swollen lymphoid tissues was not a rare sequela of typhoid inoculation.

One hazard encountered by the Army during maneuvers in this country is that of bites from black widow spiders. One report on this is made by Halter and Kuzell<sup>516</sup>. The differential diagnosis is especially important, since there may be striking confusion between this condition and a surgical condition of the abdomen and peritonitis due to ruptured peptic ulcer or acute appendicitis. Another condition encountered by Army physicians is that of strain of the rectus muscle simulating acute appendicitis. Bowers and Richard<sup>289</sup> report 8 cases of this disorder.

514 Boyd, J. S. K. Enteric Group Fevers in Prisoners of War from the Western Desert with Special Reference to Prophylactic Inoculation, *Brit. M. J.* **1** 719, 1943.

515 Bowers, W. F., and Shupe, L. Acute Appendicitis: Sequela of Typhoid Inoculation, *Mil. Surgeon* **90** 413, 1942.

516 Halter, B. L., and Kuzell, W. C. Black Widow Spider Bites in the Adult Male, *Mil. Surgeon* **92** 427, 1943.

seen in a period of six weeks at Camp Chaffee. The presence of a mass and/or ecchymosis and pain in the region of either rectus muscle is presumptive evidence of strain until proved otherwise. The mistaken diagnosis of acute appendicitis is frequent, because of pain in the lower part of the abdomen, mild fever and leukocytosis, mild nausea and rebound tenderness. In the cases presented, the two most common causes were thought to be forcible flexion of the trunk incurred while the patient was scaling a high wall and hyperextension of the trunk due to a high jump into the air.

Miss Kate A. Spencer and Miss Phoebe O. Nichols gave valuable aid in the preparation of this article.

Massachusetts General Hospital

## Book Reviews

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**Myotonias** By Alfredo Lanari Pp 277 Buenos Aires Imprenta Ferrari Hnos, Bme, 1943

In his introduction Lanari begs forbearance for the use of the single word "myotonias" as the title of his book, inasmuch as it gives the impression that the various diseases in which the symptom is prominent are nosologically related. But he goes on to say that the work of other investigators and his own studies point in that direction. He then discusses the history of this symptom since the first description by Bell, in 1832. In the analysis of the etiology he separates the hereditary from the acquired myotonias. In the former the hereditary factor is an autosomic, dominant trait. In myotonia acquisita hypothyroidism is extremely frequent, but he considers it only an exciting factor, for even after the myotonia disappears with treatment the response of the muscles to acetylcholine is the same as that in the hereditary forms. Furthermore, the author discovered evidences of status dysraphicus in both his cases of the acquired form, a condition almost universal in his entire series. He concludes that for the myotonias, as for Friedreich's disease and syringomyelia, status dysraphicus constitutes a genotypical milieu.

Lanari reports and analyzes 14 cases in which the myotonic syndrome was presented, 6 of myotonia dystrophica, 6 of Thomsen's disease and 2 of acquired myotonia. He agrees with the investigators (Batten, Gibbs and Steinert) who deny any relationship between myotonia dystrophica and pseudohypertrophic dystrophy. He calls attention to the suggestion of others that Thomsen's disease is an incomplete form of myotonia dystrophica in which the muscular dystrophy has not yet appeared, but affirms that he has not been able to reach that conclusion from the study of his own cases. He points out that the idiomuscular reaction is the characteristic of myotonia, while myoedema is only incidental and may be due to coincidental factors (i.e., hypothyroidism in hypertrophia musculorum vera). From the study of the electromyograms and the action of drugs, such as prostigmine, acetylcholine and epinephrine, injected into the artery with the circulation cut off, Lanari concludes that myotonia is determined in the muscle itself. But he does not deny the possibility that there may be an underlying lesion in some part of the nervous system, perhaps the diencephalon.

Every phase of the syndrome is carefully presented, and an attempt is made to cover any debatable point in the etiology, pathology and semeiology. The chapter

on treatment is up-to-date and conservative. The book is written in concise Spanish and is well illustrated. In the opinion of the reviewer it is a fine addition to the literature on the subject. The bibliography is ample.

**Frontiers in Cytochemistry The Physical and Chemical Organization of the Cytoplasm** Edited by Normand L. Hoerr Price \$3.50 Pp 334, with portrait and 98 figures Lancaster, Pa. Jaques Cattell Press, 1943

This book consists of a series of fourteen articles which represent, in expanded form, papers contributed to a symposium that was held at the University of Chicago on Nov. 13, 1942, in honor of the seventy-fifth birthday of Prof. R. R. Bensley. The general subject is the chemical structure of cytoplasm, which is seen to present a variety of interesting aspects, both theoretic and practical. Among the former are the isolation of mitochondria for analysis, the study of protoplasmic fibrils by means of the electron microscope and the use of the ultracentrifuge and of electrocataphoresis in fresh discoveries of substances that lie in the twilight zone between living and dead material. Among the practical aspects are carcinogenesis in epithelium and chromatolysis in motoneurons. The series is introduced by a foreword by Hoerr and an appreciation by Cowdry and closes with a review of the chemistry of cytoplasm by Professor Bensley. It makes an attractive volume for the medical reader interested in biology.

**Afecciones del endocardio Contribucion al estudio anatomico clinico de las afecciones del endocardio** Theses by Dr. Manuel Perea Munoz Paper Pp 363 Buenos Aires, Argentina Universidad Nacional, 1942

This work is the result of painstaking study and research on the part of the author. The material was obtained from 1,000 autopsies, 206 of which revealed endocardial disease. There are many photographs of specimens and of histologic sections throughout the book, serving to illustrate and emphasize concepts brought out by the author. A fairly successful attempt has been made to classify and to discuss all diseases of the endocardium from the point of view of etiology and pathologic anatomy. The bibliography is extensive and complete, covering the literature on the subject in different languages.

## TRANSFUSION REACTIONS CAUSED BY ACQUIRED INTRAGROUP INCOMPATIBILITIES

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Routine grouping and cross matching of blood of donors and of recipients<sup>1</sup> enable the laboratory to supply compatible blood for most transfusions. However, blood that is satisfactory by the usual technic may produce serious, even fatal, hemolytic reactions in patients receiving repeated transfusions<sup>2</sup>. It has been shown that such intragroup incompatibilities are produced by immune isoagglutinins that develop in the recipient. The agglutininogen present in the blood of the donor is usually the Rh factor, although other factors occasionally may be responsible. Irrespective of the factor involved, the intragroup transfusion reactions in male patients are similar in that they occur after repeated transfusions.

Repeated transfusions are frequently indicated in the treatment of certain types of patients who are transferred finally to Army general hospitals. Therefore, it seems likely that it will be in such institutions that the problem of acquired intragroup incompatibilities will be met most often. From Nov 8, 1941 to Aug 31, 1942 there were 2 severe and 25 mild reactions to transfusion at the O'Reilly General Hospital. During this period, 231 transfusions were given to a total of 46 patients. Fourteen of these patients received from 5 to 28 transfusions for a total of 177. Seven of the 14 had no reaction. The other 7 suffered 26 of the 27 reactions. There were 16 pyrogenic reactions (3 major and 13 minor), 7 allergic reactions manifested by mild urticaria, 2 reactions consisting of transient precordial pain and 2 hemolytic reactions. The 2 hemolytic reactions occurred in the same patient after his twenty-seventh and twenty-eighth transfusions and were the result of acquired intragroup incompatibility, in which the agglutininogen was the Rh factor. After the experience with this case, the inade-

quacy of routine cross matching for demonstrating acquired isoagglutinins was recognized. Thereafter, when prospective recipients were known to have received more than 5 transfusions the centrifuge technic for cross matching was adopted as a routine procedure. Despite this precaution, a second patient suffered a severe reaction from blood that was compatible according to these additional laboratory procedures. The study of these 2 cases serves to illustrate the ways of preventing reactions due to acquired intragroup incompatibility, a transfusion hazard that has been investigated and overcome largely within the past two years.

### HISTORICAL ASPECTS

In 1940 Landsteiner and Wiener<sup>3</sup> reported an agglutinable factor in human blood detectable by immune serums for *Macacus rhesus* blood. Blood agglutinated by this immune serum is designated as being Rh positive blood, that not agglutinated by it is designated as being Rh negative. Subsequently, 3 cases of hemolytic transfusion reaction were reported in which it was found that the patient's serum contained irregular agglutinins giving reactions unrelated to the four blood groups<sup>4</sup>. These reactions corresponded exactly with the reactions on human bloods of the immune serums for *Macacus rhesus* blood. Wiener and Peters explained the hemolytic reactions as follows: "Their patients, all being Rh negative and receiving Rh positive blood by repeated transfusions, responded to these injections by producing immune isoantibodies. While at first the foreign Rh positive blood was eliminated from the body without the occurrence of noticeable symptoms, after the isoantibodies were formed subsequent transfusions resulted in hemo-

From the Laboratory and Medical Services, O'Reilly General Hospital, Springfield, Mo.

1 Methods for Laboratory Technicians, War Department, Technical Manual 8-227, Washington, D. C., Government Printing Office, 1941, p. 301.

2 Wiener, A. S. Hemolytic Transfusion Reactions. I. Diagnosis with Special Reference to the Method of Differential Agglutination, *Am J Clin Path* 12: 189 (April) 1942.

3 Landsteiner, K., and Wiener, A. S. An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood. *Proc Soc Exper Biol & Med* 43: 223 (Jan) 1940.

4 Wiener, A. S. and Peters, H. R. Hemolytic Reactions Following Transfusions of Blood of the Homologous Group, with Three Cases in Which the Same Agglutininogen Was Responsible, *Ann Int Med* 13: 2306 (June) 1940.



lytic reactions of progressively increasing severity, in one case resulting in death"

Recently it has been pointed out that anti-Rh serums are not identical and that blood from a single person may be Rh positive according to one serum and Rh negative when tested with another serum<sup>5</sup>. This introduces one factor which makes it impractical for a laboratory with limited facilities to attempt to prepare a roster of donors with Rh-negative blood for use in cases in which repeated transfusions are indicated for persons with Rh-negative blood. Furthermore, not all acquired intragroup incompatibilities are explained on the basis of the Rh factor. It has been demonstrated that intragroup reactions occur in patients with Rh-positive blood after repeated transfusions<sup>6</sup>. In the blood of such a patient, compatible with that of a donor by ordinary cross matching, an irregular agglutinin is demonstrable in vitro by a centrifuge technic at refrigerator or body temperature. Finally, even these special laboratory methods fail to demonstrate the presence of acquired agglutinins in some cases and the hemolytic transfusion reaction gives the first sign of the existence of the incompatibility<sup>6</sup>.

#### REPORT OF CASES

##### CASE 1—*Anti-Rh agglutinin*

C P, a 25 year old white man with five years of service, was admitted to O'Reilly General Hospital May 1, 1942, by transfer from a station hospital which he had entered April 14, 1942, because of a severe sore throat. For this he had received sulfanilamide (1 Gm four times a day). On April 22 the treatment was discontinued because of gingival bleeding and ulcers of the oral mucous membrane. At this time the red blood cells numbered 2,190,000 per cubic millimeter and the white cells 1,850, the hemoglobin content was 7 Gm per hundred cubic centimeters. Between April 22 and May 1 he was given 5 blood transfusions of about 300 cc each, without incident. The past medical history disclosed that the patient had a penile chancre in October 1941. A dark field examination at that time gave positive results, and routine antisyphilitic therapy was started immediately. The last intravenous injection of an arsenical was administered April 30, 1942. At no time was the Kahn or Wassermann reaction positive. He had received a yellow fever inoculation (lot 335) in February 1942.

On physical examination the patient was acutely ill and there was pallor of the skin. The temperature was 101 F, the pulse rate 96 and the respiratory rate 24. There were large necrotic ulcers scattered through the mouth, and abundant pus exuded from the gingival

5 (a) Wiener, A S. Hemolytic Transfusion Reactions. III Prevention, with Special Reference to the Rh and Cross-Match Tests, *Am J Clin Path* 12:302 (June) 1942. (b) Davidsohn, I, and Toharsky, B. The Rh Blood Factor. An Antigenic Analysis, *ibid* 12:434 (Aug) 1942.

6 Wiener, A S, Silverman, I J, and Aronson, W. Hemolytic Transfusion Reactions. II Prevention, with Special Reference to a New Biological Test, *Am J Clin Path* 12:241 (May) 1942.

margins. The heart and lungs were within normal limits. The blood pressure was 122 systolic and 80 diastolic. The liver and spleen were not palpable. Numerous petechiae were scattered over the body surface.

Laboratory studies on May 1, 1942 revealed 2,320,000 red blood cells per cubic millimeter and 1,050 white cells and 92 Gm of hemoglobin per hundred cubic centimeters. A differential white cell count showed 82 per cent mature lymphocytes, with no immature forms. The platelet count was 64,000, the coagulation time six minutes and fourteen seconds, the bleeding time thirty-five seconds and the icterus index 6. The Kahn reaction

TABLE 1—*Transfusion Record of C P (Group O)\**

Date	Donor	Group	Amount, Cc †	Reaction
5/ 4/42	BW	O	500	None
5/ 6/42	PEN	O	500	None
5/ 8/42	ORA	O	500	None
5/10/42	SRA	O	500	None
5/12/42	RIA	O	500	None
5/14/42	DPB	O	500	None
5/16/42	HJO	O	500	None
5/18/42	LRO	O	500	None
5/21/42	DLD	O	500	None
5/23/42	LHR	O	500	None
5/25/42	JSL	O	500	None
5/28/42	EMC	O	500	None
5/31/42	HWO	O	500	None
6/ 3/42	GMD	O	500	Reported on chart as "slight" reaction following transfusion (nature not stated)
6/ 5/42	LWH	O	500	None
6/ 8/42	WCK	O	500	None
6/10/42	LEA	O	500	None
6/12/42	OJFE	O	500	None
6/14/42	WDK	O	500	None
6/18/42	PH	O	500	None
6/21/42	PJL	O	500	None
6/24/42	FAP	O	500	None
6/27/42	GCT	O	500	None
6/30/42	RWH	O	500	None
7/ 3/42	DJM	O	500	None
7/ 7/42	RJE	O	500	None
7/ 9/42	WNO	O	500	Severe chill 1 hour after ward, temperature 104 F, patient noticed urine was dark after chill
7/12/42	EAD	O	3 to 5	Following introduction of needle and giving of 5 cc of blood, patient complained of tenseness in mediastinum, difficulty in breathing and pain in lumbar region, presented clinical picture of mild shock, transfusion immediately stopped, temperature rose to 103 F

\* From April 22, 1942 to May 2, 1942 five transfusions of 300 cc each were given every other day at a station hospital.

† The indirect citrate method was used for all transfusions.

was negative. Roentgenograms of the chest and electrocardiograms gave normal findings. Aspiration biopsy of sternal marrow on June 25, 1942 showed hypoplastic marrow.

The therapeutic program consisted initially of repeated blood transfusions and administration of pentnucleotide and of yellow bone marrow. Use of the last two remedies was stopped after seven days, since no beneficial results had been obtained. Transfusions of 500 cc of blood were given every second or third day for a total of 28. The patient's blood was of group O, and that of all the donors was also of group O (table 1). On June 10, 1942, after 21 transfusions had been given, it was noted that the liver and spleen were palpable, and on June 12 jaundice became manifest. The icterus index gradually increased to 228 on July 19. The hepatitis was treated by daily administration of 1,000 cc of 15 per cent dextrose solution intravenously, administration of thiamine hydrochloride (5 mg four times a day) and

a high carbohydrate, high protein, low fat diet. With this program the jaundice, splenomegaly and hepatomegaly gradually subsided. During this period of deep jaundice transfusions (500 cc) were continued every second or third day, but the red blood count fell progressively. On July 9, 1942, one hour after a transfusion of 500 cc (donor WNO), the patient had a severe chill, the temperature rose to 104 F and he noted that his urine, which had previously been clear, became dark brown. On July 13, 1942 another blood transfusion was started. Approximately 5 to 10 cc of blood had passed into the vein when the patient complained of severe upper mediastinal tension, dyspnea, low lumbar backache and weakness. The patient obviously was in early shock. The transfusion was immediately stopped and the shock treated. No transfusions were given after July 13. Subsequent to the stopping of the transfusions there was gradual improvement in the blood picture. At the time of the patient's discharge, Feb 17, 1943, the blood counts and differential counts were essentially normal, except for the platelet count, which remained persistently between 50,000 and 60,000. A study of the bone marrow made on Aug 5, 1942 showed active hemopoiesis.

In review of the history and course of the condition, it was considered that this was a case of aplastic anemia of undetermined cause, sulfanilamide and arsenic being suspected. During the course of this illness catarrhal jaundice developed, which was not thought to be related to transfusions. It is possible, but not likely, that the anemia and the hepatic disease were caused by the same unknown etiologic agent.

After the first reaction (July 9, 1942), the cross match was checked at room temperature and the compatibility of the donor's blood by that method was confirmed. After the second severe reaction it was felt that further studies were indicated. Within an hour after the reaction, 2 drops of the patient's serum and 1 drop of a suspension of the donor's blood cells were placed in small test tubes. One was incubated at 37 C for thirty minutes and then centrifuged at 500 revolutions per minute for one minute. Another was placed in ice water in the refrigerator for five minutes and then centrifuged in ice water for one minute at 500 revolutions per minute. In both of these tubes the donor's cells were agglutinated, and some agglutination occurred at room temperature after prolonged standing (one hour). Twenty-seven days later samples of blood from the patient and from donor WNO were sent to Dr I Davidsohn, of Chicago, who found that the patient's blood was of group O and Rh negative and demonstrated the presence of anti-Rh agglutinin. Donor WNO was found to have blood of group O and Rh positive. Donor EAD was no longer available for study. This is a case of the development of anti-Rh agglutinins in Rh-negative blood. At first there was simply destruction of the transfused blood, as evidenced by the progressive fall in the red blood cell count despite the transfusions. Finally, hemolytic reactions occurred when the patient was given transfusions with Rh-positive blood.

#### CASE 2—*Unidentified agglutinin*

C J, a 27 year old soldier, was transferred to O'Reilly General Hospital March 28, 1942 from a station hospital which he had entered March 4, 1942 because of persistent bloody diarrhea. About Feb 18, 1942 he noted the onset of frequent watery stools that were streaked with blood and mucus. The stools, numbering ten to twelve per day, were preceded by severe abdominal cramps. Physical examination and laboratory studies led to a diagnosis of chronic ulcerative colitis.

The therapeutic program consisted primarily of a nutritious diet and supplementary vitamins. Camphorated tincture of opium contributed little toward controlling the diarrhea. A course of sulfaguanidine caused no improvement. On May 17, 1942, the total serum protein was 6.9 per cent, albumin 2.8 per cent and globulin 4.1 per cent. Transfusions of whole blood and of plasma were given to combat mild secondary anemia and the reversed albumin-globulin ratio of the serum. The patient's blood was of group AB, and that of the donors was of groups AB and group O. He suffered occasionally from urticaria following blood transfusions, but no difficulty was experienced in obtaining compatible donors until Aug 11, 1942. At this time the patient's serum hemolyzed the red cells of two donors with blood of group AB, but the blood of the third donor (SPS) was compatible and the patient had no ill effect from the transfusion other than slight itching of the skin. Between August 11 and September 3, 10 transfusions of plasma were given while the laboratory searched vainly for a donor. Fifteen consecutive donors with blood of group AB were rejected because the patient's serum hemolyzed the donor's red cells (only at incubator temperature). On September 3 a donor (LFF) was found whose blood was compatible on cross matching at room temperature and by the centrifuge technic at refrigerator and incubator temperatures. The transfusion was given over a period of two and one-half hours. Thirty minutes after its completion there was a severe chill, and the temperature rose to 106.4 F. Urine collected two hours after the chill showed no hemoglobin, while blood obtained at the same time gave an icterus index of 5. The cross matchings were repeated, and there was no agglutination or hemolysis at room, refrigerator or incubator temperatures.

On September 7, samples of blood from the donor (LFF) and the patient were sent to Dr I Davidsohn, who found them both to be of group AB and Rh positive. The patient's serum did not agglutinate blood of subgroups A, B or A<sub>2</sub>B, nor did it agglutinate or hemolyze the offending donor's blood at room temperature, 37 C or refrigerator temperature. The patient's blood did, however, contain a cold agglutinin acting at temperatures from 2 to 10 C. There is little likelihood that this cold agglutinin caused the reaction, because the donor's blood was collected, transported and administered warm. There remained the remote possibility that the patient had become sensitized to some constituent of the plasma he was given. Consequently, plasma of the same lot was used for cutaneous tests and for agglutination tests (including centrifuge tests). The reactions to all of these tests were negative.

In spite of the failure to demonstrate evidence of hemolysis in specimens of urine and blood collected two hours after the reaction, this is considered to be a case of acquired intragroup incompatibility in which the unidentified agglutinin was not of Rh factor origin. This warm isoagglutinin was demonstrable in vitro after the patient had received 11 transfusions and then only by use of the centrifuge technic. It produced hemolysis of the red cells of 15 consecutive donors with blood of group AB. After three weeks it was no longer demonstrable in vitro, and its presence was demonstrated only presumptively, by the transfusion reaction. This is the type of

case in which a severe reaction may be prevented by employing the biologic test (to be described)

METHODS OF PREVENTION

Wiener <sup>1a</sup> has recently published methods for demonstrating acquired isoagglutinins and has advocated the use of a biologic or clinical test for the recognition of those intragroup incompatibili-

TABLE 2—*Transfusion Record of C P J (Group AB)*

Date	Donor	Group	Amount, Ce *	Reaction
4/ 7/42	TBS	AB	500	None
4/11/42	WFS	O	450	None
4/14/42	AJD	O	500	None
4/16/42	OJO	O	350	Mild urticaria
4/19/42	RED	O	500	None
4/22/42	GD	O	500	None
4/27/42	DWMeG	O	300	None
5/10/42	TKE	O	500	None
5/21/42	TDH	AB	500	Severe urticaria
6/ 3/42	IJM	AB	500	Mild urticaria
7/27/42	OFS	AB	500	Severe urticaria
8/11/42	SPS	AB	370	Mild urticaria, temperature 101 F after transfusion
8/14/42	Plasma		500	None
8/15/42	Plasma		500	None
8/16/42	Plasma		500	None
8/17/42	Plasma		500	None
8/18/42	Plasma		500	None
8/19/42	Plasma		500	None
8/20/42	Plasma		500	None
8/21/42	Plasma		500	None
8/22/42	Plasma		500	None
8/23/42	Plasma		500	None
9/ 4/42	LIT	AB	500	Chill, temperature 104.6 F 30 minutes after transfusion

\* The indirect citrate method was used for all transfusions

ties that cannot be detected in vitro. This laboratory has adopted modifications of these tests and is using the following system for obtaining donors for patients who have had five or more blood transfusions

Cross Matching

- 1 Routine grouping and cross matching at room temperature (read at the end of thirty minutes)

Warm Centrifuge Test

- 2 (a) Put 1 drop of the patient's serum plus 1 drop of the donor's cell suspension in a small test tube
- (b) Put 1 drop of the patient's serum plus 1 drop of the patient's cell suspension in a small test tube
- (c) Incubate a and b at 37 C for thirty minutes and then centrifuge for one minute at 500 revolutions per minute in water at about 42 C

Cold Centrifuge Test

- 3 (a) Put 1 drop of the patient's serum plus 1 drop of the donor's cell suspension in a small test tube
- (b) Put 1 drop of the patient's serum plus 1 drop of the patient's cell suspension in a small test tube
- (c) Place in ice water for five minutes and then centrifuge one minute at 500 revolutions per minute in ice water

Reading

- 4 Take the tubes from the centrifuge and gently agitate. Pour a drop from each tube on a slide and examine microscopically for agglutination

Interpretation

- 5 When no agglutination occurs in any of the tubes, the donor's blood is considered compatible. When agglutination occurs in either or both of the tubes containing the patient's serum and the donor's cells, no agglutination occurring in the control tubes (2b, 3b), the donor is rejected, the procedure having demonstrated the presence of isoagglutinins. When agglutination occurs in both of the tubes at refrigerator temperature (3a, 3b), the reaction is interpreted as due to a cold autoagglutinin, and the donor may be used. However, to prevent a reaction from an irregular isoagglutinin that may be masked by the action of the autoagglutinin, the transfusion officer is advised to employ a modified biologic test. The technic employed is as follows: The patient is given 50 cc of the donor's blood and is observed for one hour. During this period any urine passed is collected and examined for hemoglobin. If the patient shows no evidence of reaction in an hour and the urine no evidence of hemoglobin, the remainder of the blood is given.

The biologic test finds its greatest usefulness in demonstrating incompatibilities that are not evident in vitro. When a recipient has suffered a hemolytic reaction to a previous transfusion or when the recipient has been found by centrifuge tests to have acquired isoagglutinins for blood of the same group, the biologic test is never omitted even though the blood of the donor used is compatible by routine cross matching and centrifuge tests. Similarly, any severe reaction to a previous transfusion is sufficient indication for its use.

COMMENT

Since the centrifuge and the biologic test have been in use in this general hospital (Sept 15, 1942 to Jan 15, 1943), 108 transfusions have been given to 42 patients without serious reaction. There have been 6 allergic and 5 pyrogenic reactions (2 major, 3 minor). Seven patients have received 5 or more transfusions for a total of 63. It has been necessary to reject 18 donors because of positive reactions to centrifuge tests, and 1 patient received a biologic test because of the presence of cold autoagglutinins.

The advantage of this regimen in safeguarding patients receiving repeated transfusions in general hospitals lies in its simplicity and its inclusiveness. Although it does not provide identification of the responsible agglutinin, the regimen permits the recognition of the presence of acquired incompatibility, whether it be due to the Rh factor or to some other rarer agglutinin. Finally, it makes possible the selection of a donor whose blood lacks the offending agglutinin.

# THIAMINE METABOLISM

WITH PARTICULAR REFERENCE TO THE ROLE OF THE  
LIVER AND KIDNEYS

ROBERT H WILLIAMS, M.D., AND GROSVENOR W BISSELL, M.D.

WITH THE ASSISTANCE OF JEAN B PETERS

BOSTON

Banga, Ochoa and Peters<sup>1</sup> have shown that most of the biologic activity of thiamine is exerted only when the latter exists in the form of diphosphothiamine. All of the nucleated cells of the body have been thought to possess the power to convert thiamine to diphosphothiamine,<sup>2</sup> the liver<sup>3</sup> and the kidney<sup>4</sup> possessing this activity more than the other tissues. Furthermore, these organs have a greater capacity for the dephosphorylation of diphosphothiamine.<sup>5</sup>

These observations introduce an important query as to whether with severe disease of the liver or kidneys there is a disturbance in thiamine metabolism. Certain studies that have been made suggest that such may be the case. For example, Borson<sup>6</sup> found that 3 patients with hepatic cirrhosis, excreted a distinctly larger percentage of a standard test dose of thiamine than did his normal subjects. He suggested that the damage of the liver might cause a decrease in the phosphorylation of thiamine and lead to a decrease in the storage and utilization of this vitamin. A somewhat similar phenomenon was observed by Williams, Egana, Robinson, Asper and Dutoit<sup>7</sup> in

thyrotoxic patients. They found that some of these patients excreted normal amounts of thiamine in the urine even when the diphosphothiamine content of the blood was subnormal. The frequent existence of impaired hepatic function in thyrotoxicosis and the resulting decrease in the phosphorylation capacity of the liver were suggested as one explanation for the inefficient thiamine economy.

Thiamine deficiency is often present in patients with hepatic cirrhosis. A history of a low thiamine intake is usually obtained, but this may not be the only factor involved in the reduction of storage of the vitamin. Since thiamine is used in the treatment of hepatic cirrhosis, it is of interest to know more about its utilization in these patients.

Less attention has been paid to the relationship of disease of the kidney to thiamine metabolism. However, it has been observed in patients with renal disease<sup>8</sup> and with congestive heart failure<sup>9</sup> that a subnormal quantity of a test dose of thiamine is excreted.

In an effort to elucidate further the role of the liver and the kidneys in thiamine storage, we have studied certain phases of thiamine metabolism in persons with severe disease of these organs.

## PLAN OF STUDY

It was our belief that if the liver and the kidneys play an important role in the phosphorylation of thiamine it might be possible to demonstrate an impairment in this process in persons with severe disease of the liver or kidneys by administering a standard amount of thiamine and determining the blood levels of it frequently. Furthermore, the capacity for dephosphorylation perhaps can be estimated by administering a standard amount of diphosphothiamine and comparing its rate of breakdown with that in health.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School

1 Banga, I., Ochoa, S., and Peters, R. A. Pyruvate Oxidation in Brain. Active Form of Vitamin B<sub>1</sub> and Role of C4 Dicarboxylic Acids, *Biochem J* **33** 1109, 1939

2 Goodhart, R. S., and Sinclair, H. M. Estimation of Cocarboxylase (Vitamin B<sub>1</sub> Diphosphate Ester) in Blood, *Biochem J* **33** 1099, 1939

3 Ochoa, S. Enzymic Synthesis of Cocarboxylase in Animal Tissues, *Biochem J* **33** 1262, 1939

4 Westenbrink, H. G. K., and Goudsmit, J. Investigations on the Aneurin and Cocarboxylase Content of Animal Tissues, Estimated by the Thiochrome Method, *Enzymologia* **5** 307, 1938

5 Ochoa, S., in Evans, E. A., Jr. The Biological Action of the Vitamins. A Symposium, Chicago, University of Chicago Press, 1942, pp 17-42

6 Borson, H. J. Clinical Application of the Thiochrome Reaction in the Study of Thiamin (Vitamin B<sub>1</sub>) Deficiency, *Ann Int Med* **14** 1, 1940

7 Williams, R. H., Egana, E., Robinson, P., Asper, S. P., and Dutoit, C. Alterations in Biologic Oxidation in Thyrotoxicosis. I. Thiamine Metabolism, *Arch Int Med* **72** 353 (Sept) 1943

8 Najjar, V. A., and Holt, L. E., Jr. Studies in Thiamin Excretion, *Bull Johns Hopkins Hosp* **67** 107, 1940

9 Robinson, W. D., Melnick, D., and Field, H., Jr. Urinary Excretion of Thiamin in Clinical Cases and Value of Such Analyses in Diagnosis of Thiamin Deficiency, *J Clin Investigation* **19**:399, 1940

All of the subjects with severe disease of the liver had Laennec's cirrhosis. They had had pronounced ascites, but at the time the test was performed little or no fluid was present. No patient was jaundiced at the time of the test. No more than a slight anemia was present in any subject, and there was no leukocytosis. Although several of these patients were probably deficient in thiamine at the time they were admitted to the hospital, each patient was given 10 mg or more of thiamine hydrochloride per day for at least one week. In an effort to avoid having these patients supersaturated with thiamine at the time of the test, the supplementary thiamine was not given for at least three days preceding the test. Evidence of pronounced impairment of hepatic function was secured by means of the hippuric acid test and the bromsulphalein test. All patients had been hospitalized for several weeks preceding the test, and on the day of the latter they were kept in bed in a fasting and resting state.

All of the subjects with severe disease of the kidneys had well defined chronic nephritis with pronounced uremia. None of these patients had more than a mild degree of congestive heart failure. The same precautions for avoiding thiamine deficiency were taken as in the group with cirrhosis. There was little deviation of the blood from normal, except for moderate anemia in 1 patient.

The normal subjects were college students. On the day of the test the student came to the hospital without breakfast and with as little exertion as possible. He then lay down for thirty minutes before the test was begun and remained in a basal condition until the test was completed.

After a fasting specimen of blood was taken, 15 mg of thiamine hydrochloride was injected intravenously during a period of exactly two minutes.<sup>10</sup> Immediately after the injection a sample of blood was taken from the opposite arm. Samples, about 15 cc each, were taken subsequently at six minutes, fifteen minutes and one hour. Twice this amount was obtained as the fasting specimen in order that a thiamine recovery experiment could be performed. Potassium oxalate was used as an anticoagulant, the final dilution being 0.2 per cent. Immediately after collection each sample of blood was placed in a pan of ice and kept there until the analysis for the thiamine and diphosphothiamine was begun, about fifteen to thirty minutes later.

The experiment was repeated with other groups of normal, cirrhotic and nephritic persons, 15 mg of cocarboxylase<sup>11</sup> (diphosphothiamine) being used instead of thiamine. In this experiment the blood cells and the plasma were analyzed individually for the content of thiamine and diphosphothiamine.

The normal subjects were studied also for changes in the thiamine and diphosphothiamine levels of the blood after the administration by mouth of 15 mg of thiamine in about 3 ounces (90 cc) of water.

Immediately on the completion of each test the subject was requested to empty his bladder. The urine was preserved with glacial acetic acid and analyzed for thiamine.

#### *Methods of Thiamine and Diphosphothiamine Analysis*

—The method employed for the estimation of thiamine

10 Originally the test dose was 5 mg, but it was increased to 15 mg because the former amount did not cause as much change in the thiamine level of the blood as we desired. We preferred not to use a larger dose than necessary.

11 The cocarboxylase was supplied by Merck & Co, Inc.

in the urine was described by Egana and Meiklejohn.<sup>12</sup> This method is a modification of the ones used by Jansen,<sup>13</sup> by Hennessey and Cerecedo<sup>14</sup> and by Harris and Wang.<sup>15</sup> It depends on the oxidative conversion of thiamine to thiochrome in the presence of alkaline ferricyanide, giving a bluish fluorescence under ultraviolet radiation, which can be quantitated by a comparison with a set of standards. This method has proved to be relatively accurate for the estimation of thiamine in the urine. The total twenty-four hour excretion of normal persons has been found to range from 35 to 250 micrograms.

In the estimation of the thiamine and the diphosphothiamine content of blood we have used the methods of Egana and Robinson.<sup>16</sup> The technic is similar to that for the determination of thiamine used on urine. The content of diphosphothiamine in the blood is similar to that in the urine. It is estimated on the same specimen of blood as is used for the determination of thiamine. This is possible because diphosphothiamine is converted into diphosphothiochrome in the presence of alkaline ferricyanide and the diphosphothiochrome can be separated from thiochrome, owing to the insolubility of the former in isobutyl alcohol. The standards for diphosphothiochrome are prepared by running known amounts of diphosphothiamine through the same procedure as the unknown. The amount of blue fluorescence is compared with standards, as in the case of thiochrome, and thereby the amount of diphosphothiamine determined.

Great care must be taken to avoid any hemolysis, since it has been our experience as well as that of others<sup>17</sup> that this leads to large errors in the estimations of thiamine and diphosphothiamine.

The thiochrome method is not as accurate when applied to blood as when applied to urine. In the former there are more interfering substances and the percentage of recovery of added thiamine is more variable. Similar difficulties are encountered with the determination of diphosphothiamine. However, these methods may be used for the estimation of pronounced relative changes such as we are presenting in this study.

## RESULTS

### *(a) Results of Administration of Thiamine —*

After the administration of 15 mg of thiamine hydrochloride by mouth to the normal subjects a rapid absorption of this substance was evidenced by a distinct rise in the thiamine level

12 Egana, E, and Meiklejohn, A P. The Estimation of Thiamine in Urine, *J Biol Chem* **141**:859, 1941.

13 Jansen, B C P. A Chemical Determination of Aneurin (Vitamin B<sub>1</sub>) by the Thiochrome Method, *Rec trav chem Pays Bas* **55** 1046, 1936.

14 Hennessey, D J, and Cerecedo, L R. The Determination of Free and Phosphorylated Thiamin by a Modified Thiochrome Assay, *J Am Chem Soc* **61** 179, 1939.

15 Harris, L G, and Wang, Y L. Vitamin Methods. Improved Procedure for Estimating Vitamin B<sub>1</sub> in Food-Stuffs and Biological Materials by Thiochrome Test Including Comparisons with Biological Assays, *Biochem J* **35** 1050, 1941.

16 Egana, E, and Robinson, P. The Estimation of Diphosphothiamine and Thiamine in Blood, to be published.

17 Owen, P S, Weissman, N, and Ferrebee, J W. Effect of Hematin upon Stability of Thiochrome in Solutions of Alkaline Ferricyanide, *Proc Soc Exper Biol & Med* **52** 59, 1943.



of the blood six minutes later (chart 1). The diphosphothiamine rose concomitantly and continued to increase for fifteen to thirty minutes, at the end of one hour it was still above normal

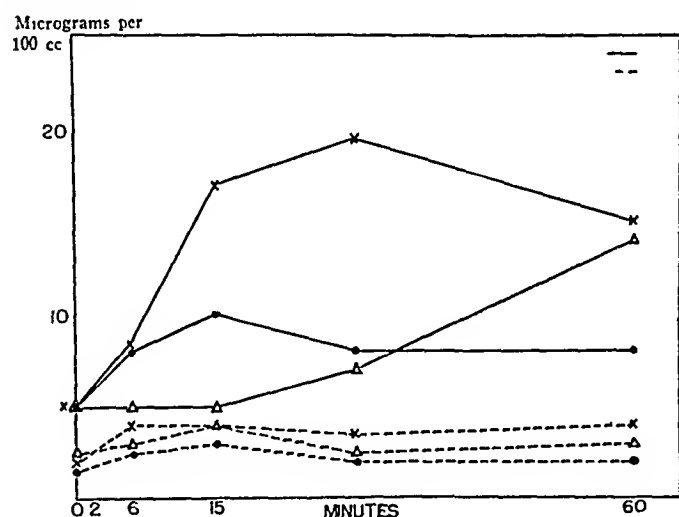


Chart 1—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of whole blood of 3 normal subjects following the oral ingestion of 15 mg of thiamine hydrochloride

The elevation of the thiamine level was of less degree than that of the diphosphothiamine, and it tended to return to normal more quickly. The amount of thiamine excreted in the urine was 0.6 per cent (range 0.3 to 0.8 per cent) of the injected dose.

When thiamine was administered intravenously to normal subjects the changes in the blood

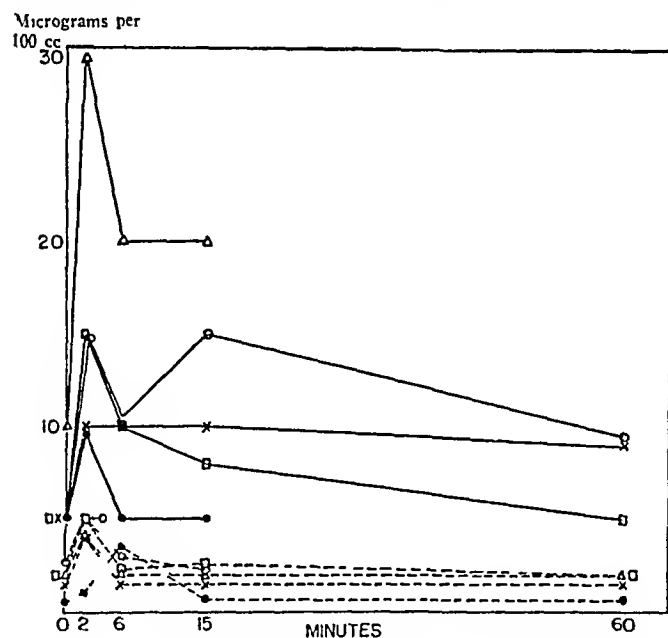


Chart 2—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) levels of the blood following the intravenous injection of 15 mg of thiamine hydrochloride into 5 normal subjects. Each injection was given during a period of two minutes.

took place much more quickly (chart 2) than when it was given by mouth<sup>18</sup>. The thiamine

<sup>18</sup> The great variability in the responses of the normal subjects, as well as in those of the abnormal ones,

level of the blood reached a peak immediately on completion of the injection but within six minutes it was normal. The rapid rate of phosphorylation was demonstrated by the large amount of diphosphothiamine found in the two minute sample. Thereafter the level declined, although in 2 instances it was still elevated at the end of an hour.

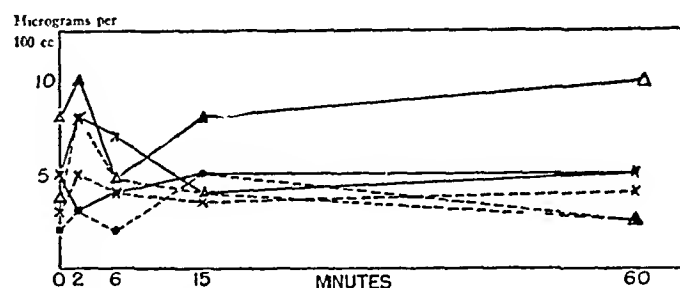


Chart 3—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) of the blood of 3 patients with hepatic cirrhosis given intravenously 15 mg of thiamine hydrochloride.

In the patients with cirrhosis (chart 3) there was distinctly less rise in the diphosphothiamine content of the blood than occurred in the normal group (chart 2). This fact plus the slightly greater rise in the thiamine level of the patients with cirrhosis suggests that phosphorylation had taken place less readily, as discussed later.

In patients with nephritis (chart 4) the rise in the thiamine level developed more slowly than in the normal subjects, but the level eventually reached about the same height. This delay may have been due to an increase in the circulation

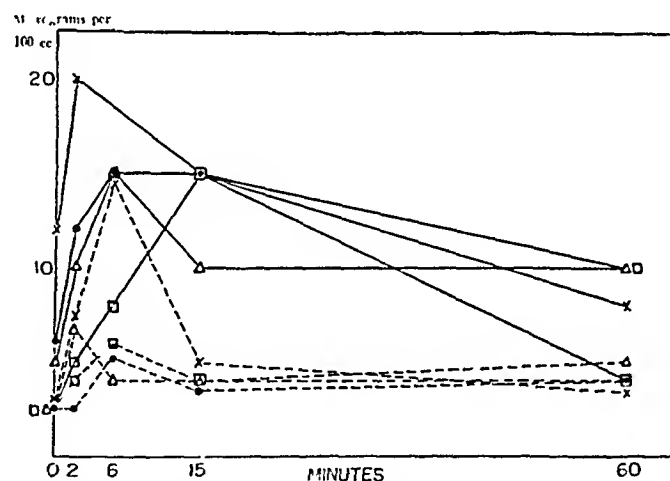


Chart 4—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) of the blood of 4 patients with chronic nephritis given 15 mg of thiamine hydrochloride intravenously.

time. The amount of diphosphothiamine formed is essentially the same as in the normal group.

Although in the three groups of subjects a striking increase in the diphosphothiamine content of the blood occurred after the injection of

is shown by the curves in the figures. Therefore, in our interpretations we have considered the trends rather than the specific curves.

thiamine, this rise was not of sufficient magnitude to account for more than 5 per cent of the amount injected. This leads to the questions as to (1) whether most of the thiamine was excreted in the urine, (2) whether it was stored in the tissues or (3) whether it was broken down to substances which do not give the thiochrome reaction.

During the hour that these tests were conducted the normal subjects excreted in the urine, on the average, 0.6 per cent of the oral dose of thiamine and 2.8 per cent of the intravenous dose. The patients with cirrhosis on the average excreted 4.7 per cent, and those with nephritis excreted 1.4 per cent. Tauber<sup>19</sup> stated that the ingestion of large amounts of vitamin B<sub>1</sub> did not result in excretion of cocarboxylase in the urine, as we have also noted. Therefore, the amount of thiamine excreted in the urine would not account for much of the administered thiamine. Furthermore, if the pyrimidine accelerator of yeast fermentation<sup>20</sup> were also included, this would not account for much more of the vitamin. As to how much of the thiamine was broken down during the period of observation, the present data are inadequate for a good estimation.

The chief consideration is storage of thiamine—its rate of storage, site and extent. The work of Borsook and associates<sup>21</sup> is of interest in this connection. They injected intramuscularly thiamine containing radioactive sulfur and determined the amount of the latter excreted in the urine and feces. One normal subject was given 16 mg daily for four days. On the first day less than 20 per cent of the injected thiamine was excreted but many times the usual amount of nonradioactive thiamine was eliminated. Six days after the last injection a total of 61 per cent of the injected radiosulfur had been recovered from the urine and 11 per cent from the feces, but 28 per cent remained unaccounted for.

Ferrebee, Weissman and Owen<sup>22</sup> found that the total amount of thiamine in the body is about

25 mg, the heart containing about 2 to 3 micrograms per gram, the skeletal muscle 0.5 microgram and the liver, kidney and brain about 1 microgram each. These investigators found that whereas a striking increase in the thiamine content of the tissues resulted from the feeding of large doses of this vitamin to rats and to human beings who were deficient in this substance, only slight increases (about 10 to 20 per cent) occurred in men maintained on a normal diet. However, it is significant that only a slight increase in the thiamine content of the tissues could cause an appreciable reduction in the thiamine content of the blood, since the normal level of the latter is about 7 micrograms per hundred centimeters, which is about one fifteenth that of the tissues.

Mason and Williams<sup>23</sup> adduced evidence that an appreciable amount of storage of thiamine may result in man. They fed 2 normal subjects 7.5 mg of thiamine hydrochloride for thirty-seven days and then placed them for five days on a diet containing 400 micrograms of thiamine and for twenty-two days on a diet which furnished 600 micrograms. Thereafter, the daily twenty-four hour excretion of thiamine was normal, as was the response to a test dose of thiamine.

Leong<sup>24</sup> found that in rats maintained on a normal stock diet the concentrations of thiamine in the various tissues was essentially the same. However, with an excessive ingestion of this vitamin the liver and heart showed a distinct increase in storage while the other organs showed little change.

Ochoa and Peters<sup>25</sup> showed that in rats and pigeons' tissues almost all of the thiamine present was in the form of cocarboxylase. This is of interest, since Banga, Ochoa and Peters<sup>1</sup> showed that essentially all of the activity of thiamine in the oxidative decarboxylation in tissue was proportional to the amount of cocarboxylase present. Furthermore, Ochoa and Peters demonstrated that the amount of diphosphothiamine was much reduced in pigeons with B<sub>1</sub> avitaminosis.

Ochoa and Peters found that thirty minutes after injection of vitamin B<sub>1</sub> into avitaminous pigeons and rats there was a pronounced accumulation of cocarboxylase in the liver, whereas

19 Tauber, H. Interaction of Vitamin B<sub>1</sub> in Enzymic Reactions, *J Biol Chem* **123** 499, 1938.

20 Gorham, A. T., Abels, J. C., Robins, A. L., and Rhoads, C. P. The Measurement and Metabolism of Thiamin and of a Pyrimidine Stimulating Yeast Fermentation Found in the Blood Cells and Urine of Normal Individuals, *J Clin Investigation* **21** 161, 1942.

21 Borsook, H., Buchman, E. R., Hatcher, J. B., Yost, D. M., and McMillan, E. Course of Thiamin Metabolism in Man as Indicated by the Use of Radioactive Sulfur, *Proc Nat Acad Sc* **26** 412, 1940.

22 Ferrebee, J. W., Weissman, N., Parker, D., and Owen, P. S. Tissue Thiamin Concentrations and Urinary Thiamin Excretion, *J Clin Investigation* **21** 401, 1942.

23 Mason, H. L., and Williams, R. D. The Urinary Excretion of Thiamine as an Index of the Nutritional Level. Assessment of the Value of a Test Dose, *J Clin Investigation* **21** 247, 1942.

24 Leong, P. C. Vitamin B<sub>1</sub> in the Animal Organization. II. A Quantitative Study of the Metabolism of Vitamin B<sub>1</sub> in Rats, *Biochem J* **31** 373, 1937.

25 Ochoa, S., and Peters, R. A. Vitamin B<sub>1</sub> and Cocarboxylase in Animal Tissues, *Biochem J* **32** 1501, 1938.



little or no increase developed in the skeletal muscle, heart or brain. The level of cocarboxylase in the liver could not be made to rise much above normal. Normal animals given thiamine had only a slight rise in the cocarboxylase of the tissues. Ochoa<sup>3</sup> obtained somewhat similar results for the *in vitro* synthesis of cocarboxylase from thiamine, using liver, brain, intestine and breast muscle of pigeons. Of these tissues the liver was the only one which exhibited a good capacity to phosphorylate added thiamine to diphosphothiamine. He found that the amount of synthesis soon reached a maximum, which was generally slightly above the normal concentration of cocarboxylase, beyond which no greater concentration of diphosphothiamine resulted, no matter how much thiamine was added. The maximal synthesis in the liver resulted in thirty to sixty minutes, but a short time thereafter the level began to drop. Brain and muscle were found to show less synthesis, but there was no decrease in the amount of cocarboxylase after the maximum was reached. Westenbrink and Goudsmit<sup>4</sup> showed that the kidneys were active in the phosphorylation of thiamine. Goodhart and Sinclair<sup>2</sup> found no evidence of the synthesis of cocarboxylase from thiamine in normal pigeon, ox and human bloods. However, when this vitamin was added to thiamine-deficient pigeon blood, marked synthesis resulted. These investigators also reported that only about 14 per cent of the total thiamine of the blood is in the plasma and essentially all of this is in the free form. On the other hand, almost all of this vitamin in the blood cells is in the form of diphosphothiamine, the white cells containing many times the amount in the red cells.

In summary, the data accumulated thus far suggest that most of the thiamine of the body is phosphorylated before it is stored, the liver and kidneys being particularly active in phosphorylation. The storage can be increased above normal, but there is a limit, which is not much above normal, beyond which no appreciable increase in the stores results. Presumably all tissues share in this accumulation, although not to an equal extent. Immediately after large quantities of thiamine have been injected the liver takes the chief responsibility for the storage and dispensation of this vitamin, permitting its concentration to increase greatly for a temporary period, during which time an establishment of equilibrium is taking place. In this interval some of the diphosphothiamine of the liver is dephosphorylated, the thiamine thereby liberated being carried by the plasma to other tissues, where it is again phosphorylated. It may also be transported in the blood cells, chiefly in the form of diphospho-

thiamine. An excess of vitamin to that stored in the body is broken down or excreted as thiamine in the urine. As the body stores go below normal, the phosphorylating activity of the kidneys increases and thereby aids in the economy of thiamine by preventing its excretion in the urine.

In attempting to interpret the various changes in the dynamic equilibrium of thiamine on the basis of studies of the blood and urine, certain facts should be emphasized. It has not been established how satisfactory the thiamine level of the blood is as an index of the content of the vitamin in the tissues. The total amount of thiamine in the blood is small, and its concentration in the tissues of the body varies. Furthermore, it is known that when large doses of the vitamin are injected the amount taken out by the tissues varies a great deal.<sup>25</sup>

The fact that in the cirrhotic patients as compared with normal there are less of a rise in the diphosphothiamine, a greater rise in the thiamine and an increased excretion of thiamine in the urine suggests that there is a decrease in the phosphorylation process. If all of the diphosphothiamine of the blood is a result of the phosphorylating activity of the blood cells it is probable that the liver has an indirect effect on this process (charts 2 and 3). It is possible that the blood cells may receive diphosphothiamine as such from the liver cells, during their passage through the liver. If this hypothesis is correct, in subjects with cirrhosis one would expect a lower level of diphosphothiamine of the blood than one observes in normal subjects, since in the former group there is a decreased blood flow through the liver and a decrease in most of the activities of the liver cells. The *in vitro* studies of Banga, Ochoa, and Peters<sup>1</sup> with various preparations of brain tissue suggested that cocarboxylase permeates the cell wall not as such but in the form of thiamine, which after entering the cell is phosphorylated. Although it is probable that the phosphorylating action of the kidney is impaired with severe renal disease, there are no definite manifestations of this reflected in the blood.

(b) *Results of Administration of Diphosphothiamine*—After the intravenous administration of 15 mg of cocarboxylase to normal subjects the plasma level rose rapidly (chart 5) and in 1 subject reached 100 micrograms per hundred centimeters. However, the rapid rate of dephosphorylation is demonstrated by the increase in the thiamine level in the two minute specimen. The thiamine content of the plasma tended to return to normal in six to fifteen minutes but the diphosphothiamine level remained elevated for more than an hour.

Concomitant with the changes in the plasma, rapid changes occurred in the blood cells (chart 6). A marked increase in the diphosphothiamine was observed in the two minute specimen. There was also a slight increase in the thiamine content

Micrograms per

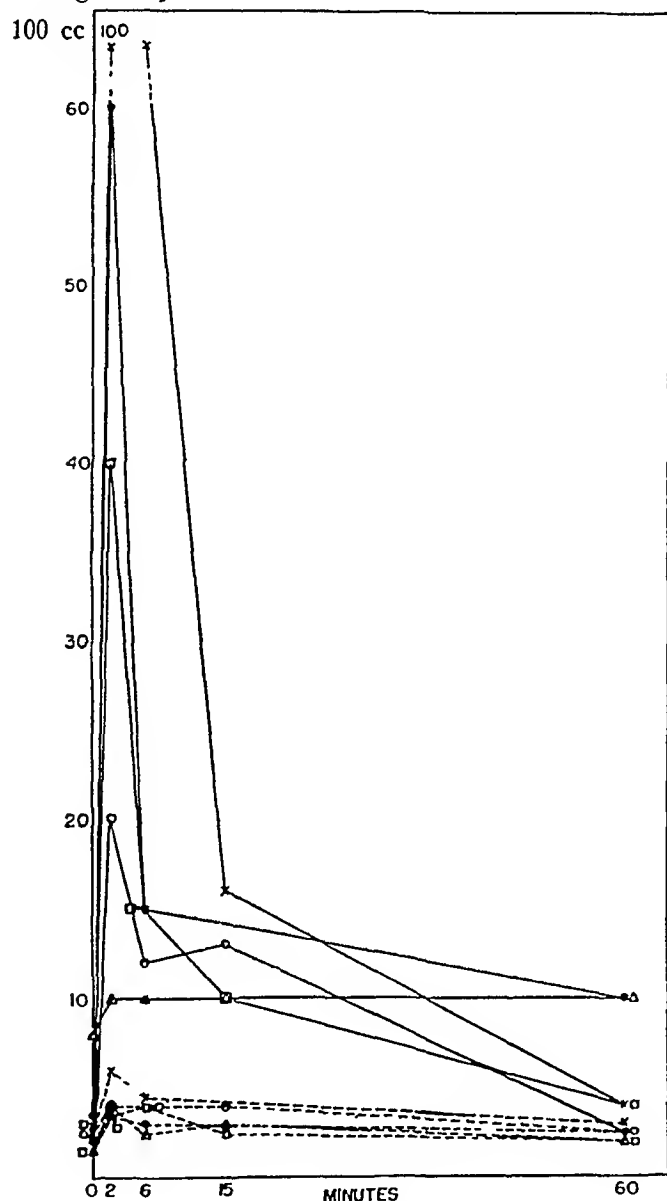


Chart 5—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of normal blood following the intravenous injection of 15 mg of cocarboxylase in 4 subjects. The injections were given during a period of two minutes.

of the cells. However, since the increase in the thiamine content of the cells and plasma was relatively small as compared with the increases in the diphosphothiamine content, one is prompted to consider either that diphosphothiamine passes through the cell membrane as such or that it is dephosphorylated and then rephosphorylated at an extremely rapid rate. The latter consideration introduces the query as to how great a part the blood cells alone play in regulating the interconversion of phosphorylated thiamine and free thiamine. Goodhart and Sinclair<sup>2</sup> could not

demonstrate *in vitro* any synthesis of diphosphothiamine from thiamine in normal blood.

Since the liver and kidneys have been demonstrated to be active in dephosphorylating as well as in phosphorylating thiamine, it is important to compare the observations on the normal subjects with those on persons with hepatic cirrhosis and severe nephritis.

In the cirrhotic group (chart 7) there was a distinctly smaller rise in the diphosphothiamine content of the plasma than occurred in the normal group. Furthermore, in the former group the diphosphothiamine had attained normal levels within six minutes, whereas with the latter group it was still elevated at the end of an hour. The diphosphothiamine content of the blood cells also tended to increase somewhat less in the cirrhotic

Micrograms per

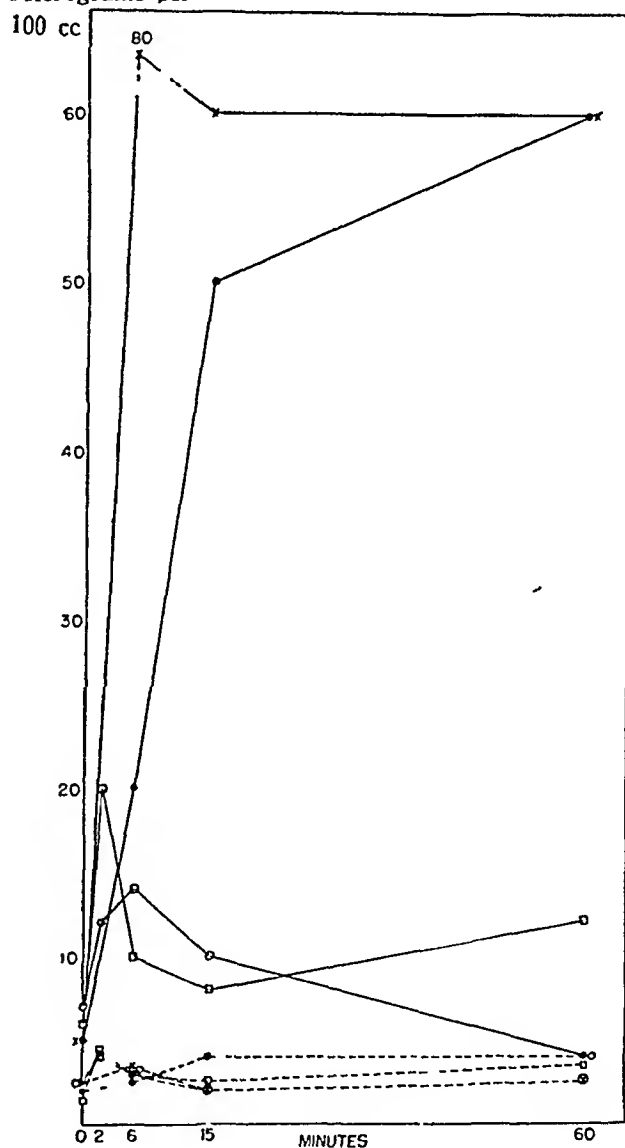


Chart 6—Same subjects as in chart 5. The curves show the changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the blood cells.

group (chart 8). On the other hand, the plasma thiamine of the cirrhotic group rose more than did that of the normal group. The changes in

the cellular thiamine were similar in the two groups

The alterations in the thiamine and diphosphothiamine blood levels in the nephritic patients (charts 9 and 10) were somewhat intermediate to those of the normal and the cirrhotic subjects

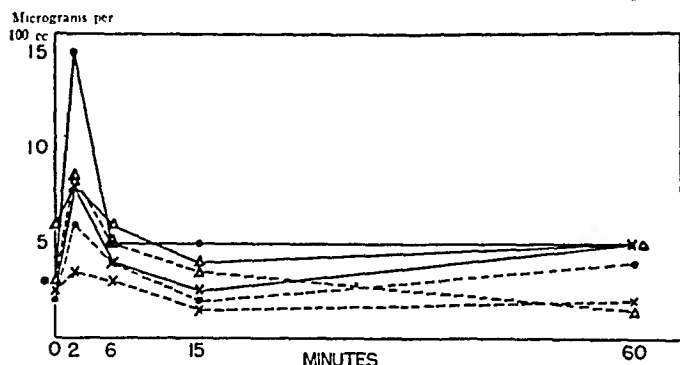


Chart 7—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the plasma of 3 patients with cirrhosis of the liver given 15 mg of cocarboxylase intravenously. Compare with chart 5

During the hour that the test was conducted the amount of thiamine excreted in the urine by the normal subjects was 1.4 per cent of the injected dose of diphosphothiamine, the nephritic group excreted 3.4 per cent. Specimens of urine were obtained from only 1 of the cirrhotic patients. However, he excreted 45 per cent of the injected dose of diphosphothiamine. The urinary thiamine was in the free form and therefore not phosphorylated. In investigating the cause of this striking diuresis of thiamine, it was discovered that one hour before the diphosphothiamine

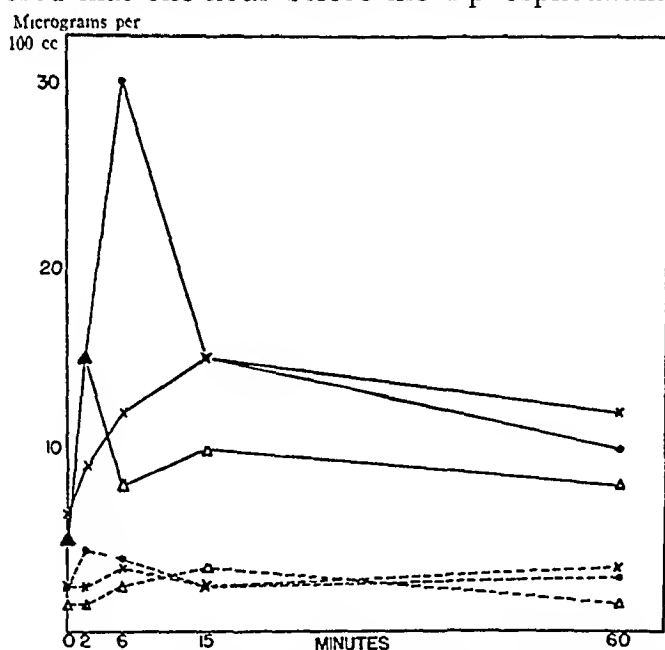


Chart 8—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the blood cells. Subjects same as in chart 7

test was made the patient had been given 2 cc of mercurphylline. Because of this, further observations were made on the effect of mercurphylline on excretion of thiamine

*Effect of Mercurphylline on the Excretion of Thiamine in the Urine*—We first studied the effect of mercurphylline on the excretion of thiamine in the urine of 2 normal subjects. We then studied its effect on 2 patients with slight congestive heart failure and 1 with Laennec's cirrhosis, since these types of patients are the ones which most often are treated with mercurphylline

The effect of mercurphylline on excretion of thiamine was observed when it was given in conjunction with 15 mg of thiamine hydrochloride. These two drugs are frequently given together, hence such a study seemed appropriate

All of the mercurphylline<sup>26</sup> was administered intravenously in 2 cc amounts two hours before

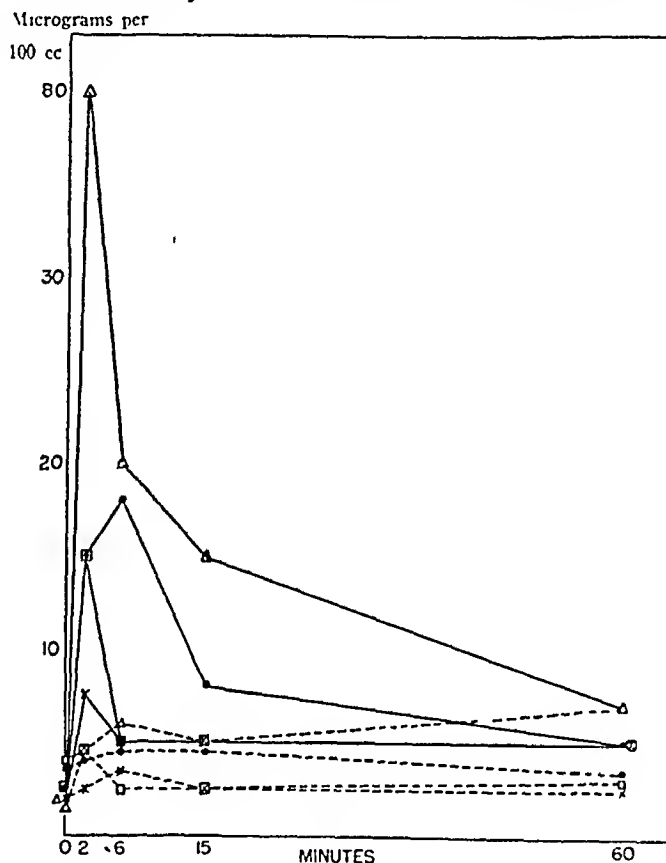


Chart 9—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the plasma of 4 patients with chronic nephritis given 15 mg of cocarboxylase intravenously

thiamine hydrochloride was administered. The latter was injected intravenously in quantities of 15 mg into all the patients with the exception of patient N. M., who received doses of 1 mg. The urine was collected in glacial acetic acid for twenty-four hours following the injection of thiamine. The same dosage of these drugs was used on the days when they were given singly as when given together

Normal subject A. M., having fully recovered from pneumonia, was transferred to the metab-

<sup>26</sup> The mercurphylline was tested for fluorescence but was found to have none. Therefore, this drug caused no apparent interference with the estimation of thiamine in the urine

olism ward. Here he was maintained on the regular hospital diet with the addition of 6 tablets of brewers' yeast daily. After one week on such a regimen, estimates were made of the daily excretion of thiamine in the urine. On the fifth day thiamine was given intravenously. In the succeeding twenty-four hours 1.9 mg of thiamine was excreted (chart 11). On the thirteenth day the subject was given mercurphylline, and during the succeeding twenty-four hours 10 mg of thiamine was excreted.

Subject S. M., convalescent from an operation for an ingrown toe nail, was transferred to the metabolism ward and was prepared with a dietary regimen, as in the case of A. M. He was given thiamine hydrochloride alone, mercurphylline alone and then the two together. The mercurphylline alone had no definite diuretic effect on the excretion of thiamine. However, when

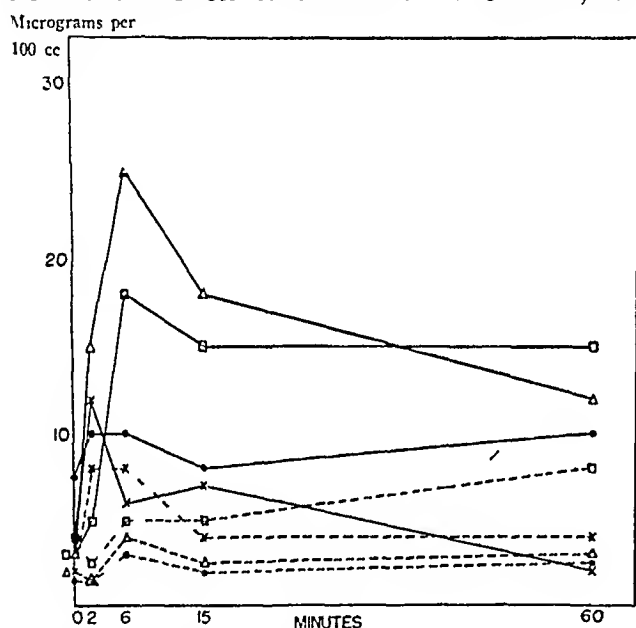


Chart 10—The changes in the thiamine (dotted lines) and diphosphothiamine (solid lines) content of the blood cells. Subjects same as in chart 9.

thiamine and mercurphylline were given on the same day there was a distinctly greater excretion of thiamine (1.06 mg) than when the latter was given alone (0.38 mg).

Patient W. E., a woman aged 70, had been in the hospital for several weeks with congestive heart failure due to arteriosclerotic heart disease. When we studied her, there was only a slight amount of heart failure. She had received subcutaneously 10 mg of thiamine hydrochloride for several weeks. The injections were discontinued one week before our studies were begun. A greater diuresis of thiamine resulted when mercurphylline was given on the same day as the thiamine (0.26 mg) than occurred when the latter was given alone (0.14 mg). However, when mercurphylline alone was given, the most pronounced diuresis of thiamine resulted (12.6 mg).

Patient M. U., a woman aged 50, had been in the hospital for several weeks with congestive heart failure because of chronic rheumatic heart disease. Her dietary intake preceding hospitalization was essentially normal, and she was maintained on a "cardiac" diet, without vitamin supplements, while in the hospital. At the time that our studies were conducted only slight manifestations of congestive failure remained. Mercurphylline given in conjunction with thiamine hydrochloride did not increase the diuresis of thiamine. However, when mercupurin alone was given, a pronounced diuresis of thiamine resulted (6.6 mg).

The patient with cirrhosis (N. M.) was a man aged 35 who had been in the hospital for several weeks. His diet had been supplemented with several vitamins, including thiamine. However, he had received no extra vitamins during the week preceding our studies. When mercurphylline was used alone there was no definite increase in the amount of thiamine excreted. However, when it was used in conjunction with thiamine, more of this vitamin appeared in the urine (0.28 mg) than was found after the administration of thiamine alone (0.14 mg).

Therefore, it is apparent that different subjects excrete variable amounts of thiamine in the urine after the administration of mercurphylline, sometimes this amount is enormous. This increased elimination of thiamine is not due alone to an increase in the volume of urine, since it was found that in several instances there was an increase in the concentration of this vitamin in the urine (chart 11). Indeed, in the urine of 2 subjects the concentration was about fifty times greater than normal, although no extra thiamine had been given for more than ten days. In spite of the excretion of large quantities of thiamine in the urine, it contained no demonstrable diphosphothiamine.

The observations which have been made thus far suggest that the large capacity of the kidney for the interconversion of thiamine and diphosphothiamine is for the conservation of the body's supply of thiamine, the kidney tubules reabsorbing most of the thiamine when its cells are deficient in this vitamin and converting it into diphosphothiamine, which, in turn, can liberate thiamine for dispensation by the blood. On the other hand, when the body is saturated with the vitamin, the kidneys permit its escape in excess quantities. When mercurphylline is administered, the tubular activity of the kidneys can be so disturbed as to permit the elimination of rather large quantities of thiamine in the urine. We found this response to vary a great deal in different subjects.

## SUMMARY AND CONCLUSIONS

Thiamine hydrochloride administered to normal subjects by mouth was found to be rapidly absorbed from the gastrointestinal tract and converted into diphosphothiamine within a few minutes

When 15 mg of thiamine hydrochloride was given intravenously to normal subjects, an immediate and striking increase in the diphosphothiamine level of the blood was observed. The rapid

When 15 mg of cocarboxylase was administered intravenously to normal subjects, an increase in the diphosphothiamine and the free thiamine of the plasma and the blood cells was observed immediately. The thiamine level rapidly returned to normal, but the diphosphothiamine remained elevated, for more than an hour in some instances. In patients with advanced cirrhosis there was also an immediate increase in the free thiamine level of the blood, but there

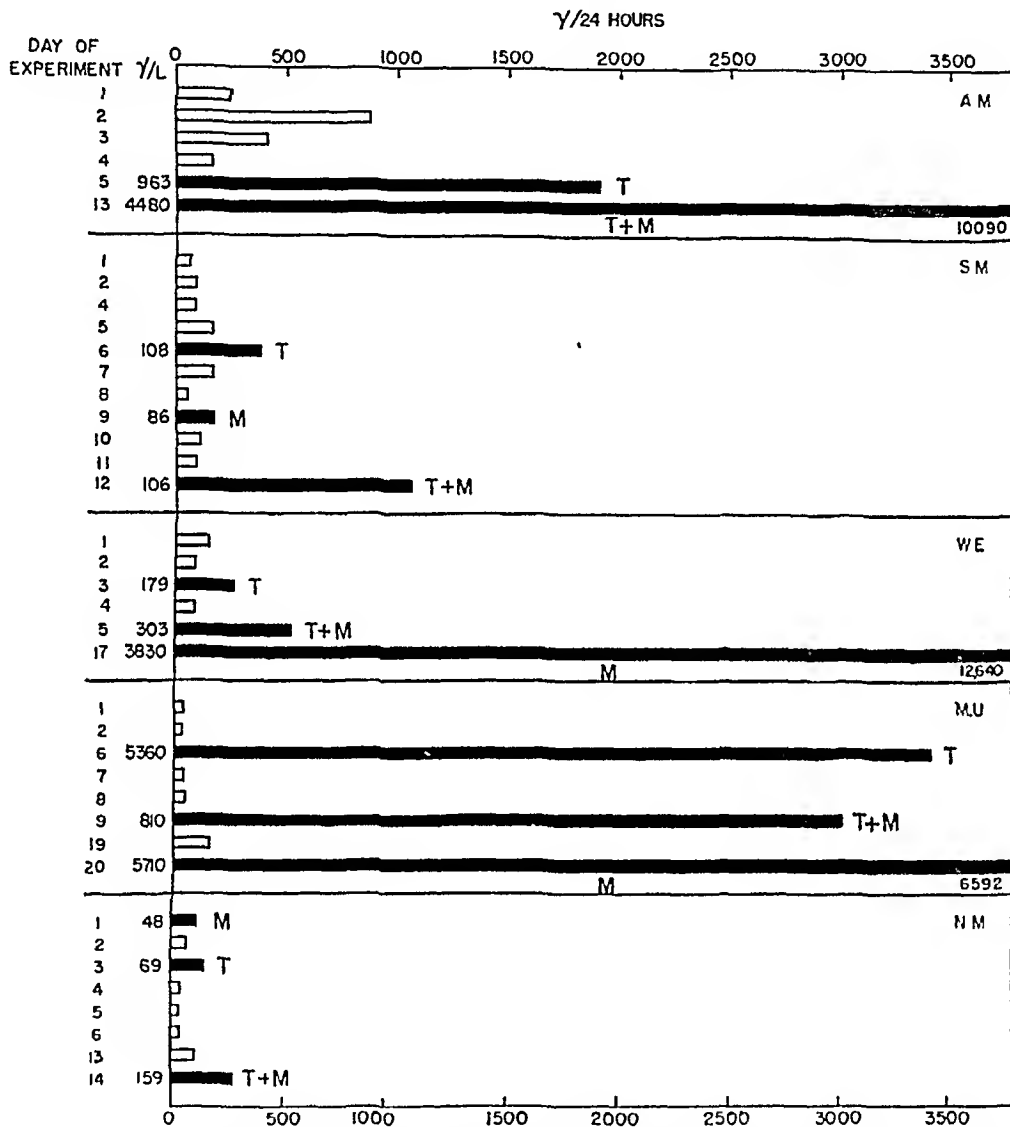


Chart 11—The changes in the twenty-four hour urinary excretion (in micrograms) of thiamine (T) following the intravenous injection of 2 cc of mercurphylline (M). When thiamine and mercurphylline were both given, the former was given intravenously two hours after the latter. The amount of thiamine hydrochloride injected was 15 mg for each patient except N M, who received only 1 mg. Note that mercurphylline caused a pronounced excretion of thiamine. This increased excretion was not due to just an increased volume of urine (Values at the left of the solid bars represent micrograms per liter.)

disappearance of the vitamin from the blood was shown by the fact that the thiamine level of the blood was normal within six minutes and the fact that the total diphosphothiamine of the blood never represented more than about 5 per cent of the injected dose.

In patients with severe hepatic cirrhosis, an impairment in the phosphorylation of the thiamine was demonstrated, but not much disturbance in this mechanism was observed in patients with nephritis.

was much less rise in the diphosphothiamine than occurred in the normal subjects. In patients with severe nephritis, the changes were intermediate between those of the normal and of the cirrhotic groups.

Mercurphylline was found to cause the excretion of a large amount of thiamine. This effect was not due alone to an increased elimination of water, because in some instances the concentration of the thiamine in the urine was many times that found in normal urine.

# TREATMENT OF GASTRODUODENAL ULCERATIVE DISEASE WITH SODIUM ALKYL SULFATE

## A PRELIMINARY REPORT

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Our results from the treatment of gastroduodenal ulcerative disease with sodium alkyl sulfate are being reported now because this new therapy has already enabled patients with ulcer to enter the armed forces, and essential war workers previously incapacitated by this disease to return to industry. Palmer<sup>1</sup> has shown that gastroduodenal ulcerative disease is the major cause of medical disability in both the English and the American forces. Since it is usually present in male adults during the years of their greatest productivity, the impairment of war effort by this prevalent disease is of serious significance. Most patients with ulcer are now being treated by a routine which has for its goal reduction of intragastric acidity. This type of medication has not been completely satisfactory because a large number of patients with gastroduodenal ulcerative disease respond inadequately to this orthodox management. To date the emphasis has been placed on the corrosive action of the acid component of the gastric juice, with almost complete neglect of the role of pepsin in the genesis of ulcer. This study was therefore undertaken to evaluate the relative importance of pepsin in the causation and the therapy of ulcer. Our objective was to determine whether inactivation of pepsin, rather than alteration of gastric acidity, would permit healing of the ulcer in a patient with gastroduodenal ulcerative disease. To achieve this goal we investigated the possible pepsin-inhibitory action of (1) the various therapeutic agents used in the treatment of patients with ulcer and (2) other compounds whose therapeutic value had not yet been investigated but which appeared promising.

### IN VITRO EXPERIMENTS

For the determination of pepsin we used a slightly modified Anson-Mirsky method<sup>2</sup> which

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1 Palmer, W. L. The Stomach and Military Service, *J. A. M. A.* **119** 1155 (Aug 8) 1942

2 Anson, M. L., and Mirsky, A. E. The Estimation of Pepsin with Hemoglobin, *J. Gen. Physiol.* **16** 59, 1932. Anson, M. L. Estimation of Pepsin, Trypsin, Papain and Cathepsin with Hemoglobin, *ibid.* **22** 79, 1938

was satisfactory in that the substrate used was reproducible and the results could be readily duplicated. This technic made it possible to demonstrate that the therapeutic agents customarily used in the therapy of ulcer inhibit "peptic" activity only through change of the hydrogen ion concentration and not by direct action on pepsin.<sup>3</sup>

These results, confirmed by Kirsner and co-workers,<sup>4</sup> led us to our next objective. This was to find a nontoxic material which would inactivate pepsin without altering intragastric acidity in order to avoid any changes in body chemistry. Dr. H. B. Bull, of the department of physiological chemistry of the Northwestern University Medical School, had shown that sodium lauryl sulfate, a surface-active agent, would denature a protein such as egg albumin in very dilute concentrations.<sup>5</sup> Since pepsin is a protein we decided to investigate the surface-active agents, such as the sulfate esters of the straight chain fatty alcohols, e. g., sodium lauryl sulfate, sodium palmityl sulfate, sodium stearyl sulfate and sodium oleyl sulfate. This group of substances was found to inhibit peptic activity in dilute concentrations without altering acidity. A combination of the aforementioned four substances, sodium alkyl sulfate, was almost as effective a pepsin inhibitor as any one of these compounds used individually. Therefore, sodium alkyl sulfate was used in our further work because it combined efficacy with availability.

### IN VIVO EXPERIMENTS

Wangensteen, Code and associates<sup>6</sup> have shown that dogs will die of gastroduodenal ulcer

3 Shoch, D., and Fogelson, S. J. Studies on Peptic Inhibition, *Proc. Soc. Exper. Biol. & Med.* **50** 304, 1942

4 Warren, I. A., Front, J., and Kirsner, J. B. The Effect of Antacid Therapy on the Peptic Activity of Gastric Juice in Man, *Gastroenterology* **1** 102, 1943

5 Bull, H. B., and Neurath, H. The Denaturation and Hydration of Proteins. II. Surface Denaturation of Egg Albumin, *J. Biol. Chem.* **118** 163, 1937

6 Walpole, S. H., Varco, R. L., Code, C. F., and Wangenstein, O. H. Production of Gastric and Duodenal Ulcers in the Cat by Intramuscular Implan-

(Footnote continued on next page)

or its complications in about thirty days if given daily injections of massive doses of histamine in a liquid petrolatum-beeswax base. Following Code's personal instructions, we were able to confirm their findings. We found the gastric secretion of these animals to have not only the high acid values reported by Wangenstein but also marked peptic activity.

The next study was to determine the effect of altering this gastric secretion so that the elevated acid component remained but the pepsin was inactivated. Another group of dogs was given daily injections of massive histamine doses but were fed in addition ten 0.1 Gm capsules of sodium alkyl sulfate at hourly intervals every day. The addition of the sodium alkyl sulfate was found to inactivate the pepsin during the twelve hour observation period without changing the high gastric acidity. The survival time of this series of dogs was prolonged to well over two hundred days in approximately half the animals.<sup>7</sup>

#### DETERMINATION OF A NONTOXIC DOSE OF SODIUM ALKYL SULFATE

Since surface-active agents, such as sodium alkyl sulfate, are believed to be toxic<sup>8</sup> and are able to denature not only pepsin but also trypsin and other proteins,<sup>9</sup> we fed 15 kilogram dogs 2 Gm of sodium alkyl sulfate per day and after ten months found no alteration in the red blood cell count, the white blood cell count, the hemoglobin, the blood proteins or the urine and no loss in body weight. Sections of liver and kidney from dogs which had been treated for seven months were normal. One of us (S. J. F.) took 1 Gm of sodium alkyl sulfate daily for eight

tion of Histamine, *Proc Soc Exper Biol & Med* **44** 619, 1940. Varco, R. L., Code, C. F., Walpole, S. H., and Wangenstein, O. H. Duodenal Ulcer Formation in the Dog by Intramuscular Injections of a Histamine Beeswax Mixture, *Am J Physiol* **133** 475, 1941.

7 Shoch, D., and Fogelson, S. J. The Effect of a Protein Denaturant on Histamine Ulcers, *Quart Bull Northwestern Univ M School* **16** 142, 1942.

8 Hober, R., and Hober, J. The Influence of Detergents on Some Physiological Phenomena, Especially on the Properties of the Stellate Cells of the Frog Liver, *J Gen Physiol* **25** 705, 1942. Smyth, H. F., Seaton, J., and Fischer, L. Some Pharmacological Properties of the "Tergitol" Penetrants, *J Indust Hyg & Toxicol* **23** 478, 1941. Epstein, S., Thronsdon, A. H., Dock, W., and Tainter, M. L. Possible Deleterious Effects of Using Soap Substitutes in Dentrifices, *J Am Dent A* **26** 1461, 1939. Hatton, E. H., Fosdick, L. S., and Calandra, J. The Toxicity and Rubefacient Action of Sulfated Higher Alcohols, *J Dent Research* **19** 87, 1940.

9 Anson, M. L. The Denaturation of Proteins by Synthetic Detergents and Bile Salts, *J Gen Physiol* **23** 239, 1939.

weeks without toxic effect. These negative results plus the results of additional studies on rats and rabbits by Dr. R. K. Richards, of the Abbott Laboratories, demonstrated that sodium alkyl sulfate was probably not toxic in the doses used by us.

#### CLINICAL OBSERVATIONS

A clinical study was undertaken on patients whose ulcers were considered intractable because the symptoms could not be controlled by any known therapy. Some of these patients had undergone one or more gastric resections. The quantity of sodium alkyl sulfate administered was governed by two factors. Our first objective was to inactivate the pepsin of the gastric secretion, and our second, to avoid toxic effects.

Study of the Wangenstein dogs, which are marked hypersecretors of a highly acid gastric juice rich in pepsin, demonstrated that 0.1 Gm of sodium alkyl sulfate would inactivate all the pepsin secreted in one hour. The human patient secretes more pepsin than the dog. This dose did not inactivate all the pepsin in the patient with ulcer but was used because clinical trial demonstrated freedom from toxicity.

Added experience has shown that a routine consisting of 0.2 Gm of sodium alkyl sulfate followed in an hour by 3 ounces (84 cc) of a milk and cream mixture gives better results.

Sodium alkyl sulfate should be administered alone because Kirsner and co-workers<sup>10</sup> have shown that the phospholipids contained in milk and other foods have an inhibitory effect on the pepsin-inactivating power of sodium alkyl sulfate. All antacids were omitted. Pain or pyrosis was controlled by gastric aspiration. When the subjective symptoms were controlled, the dietary regimen was supplemented with the customary high caloric, high vitamin ulcer diet, containing liberal portions of bland, smooth bulk or pureed vegetables. Constipation, if present, was treated by enema as indicated.

**Results**—In a series of 34 patients with ulcers considered intractable because it did not respond to previous therapy, including surgical intervention in 5 instances, there were 26 satisfactory results and 8 failures following sodium alkyl sulfate therapy. In most of the patients responding to sodium alkyl sulfate there was marked improvement within ten days, although no result was classified as a failure until the treatment had been given a thirty day trial.

#### REPORT OF CASES

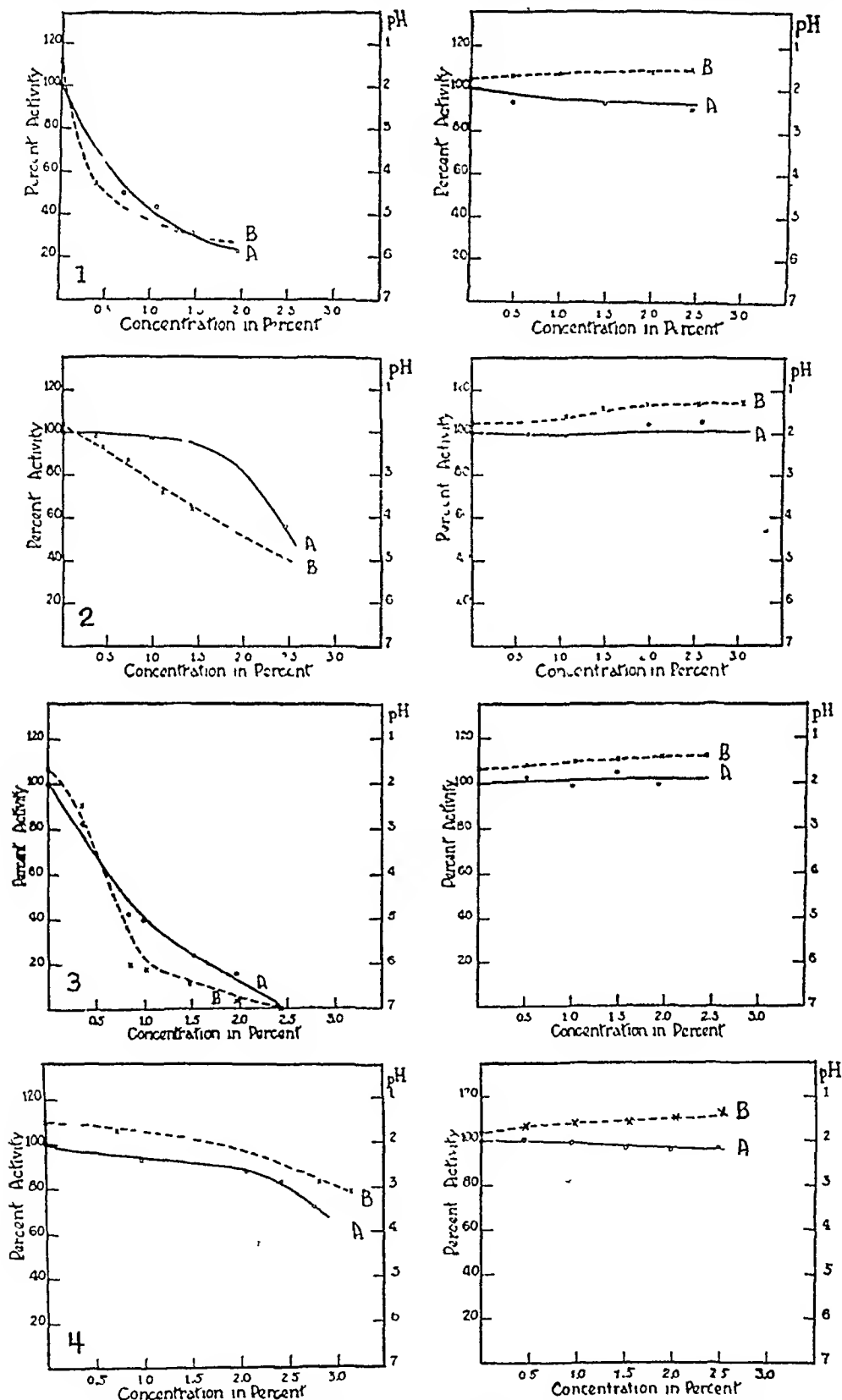
**CASE 1**—The first patient treated was 40 years old when admitted to the Cook County Hospital in August

10 Kirsner, J. B. Personal communication to the authors.



1939 He had experienced "indigestion" for ten years. A diagnosis of duodenal ulcer was made. A medical management with alkaline powders and frequent meals was started, and he was placed in a convalescent home where he remained until April 1940. He was then re-admitted to the hospital for additional therapy because his ulcer was still active.

In May 1940 a stenosing duodenal ulcer was found by surgical exploration and a partial gastric resection was done with a posterior end to side anastomosis. He was returned to the convalescent home and kept under medical management. Despite this, symptoms recurred. In April 1941 severe gastric hemorrhage necessitated rehospitalization. At this time a diagnosis of marginal



Charts 1, 2 and 3—Results of *in vitro* studies of the therapeutic agents customarily used in the therapy of gastric ulcer—aluminum hydroxide (1), aluminum phosphate (2) and magnesium trisilicate (3). In all the charts line A represents the activity of pepsin and line B the pH. The graphs shown at the left represent the result when the agent was unbuffered, those at the right, the result when the agent was buffered. All three sets of charts show that increasing concentration of the agent decreases peptic activity only when the agent is unbuffered.

Chart 4—Increasing concentration of gastric mucin decreases peptic activity only when the gastric mucin is unbuffered.

ulcer was confirmed by roentgenogram. A radical subtotal resection was done in July. The patient returned to the convalescent home, where he was kept under ulcer management. His symptoms recurred in two months and could not be controlled despite strict adherence to the antacid routine at the sanatorium.

He was readmitted to the Cook County Hospital in April 1942, where the diagnosis of marginal ulcer was confirmed by gastroscopic examination. The alkaline powders were replaced by 0.1 Gm of sodium alkyl sulfate on the half hour with a milk and cream mixture on the hour. On April 15, after two weeks of sodium alkyl sulfate therapy, the patient had practically no pain, and gastroscopic examination showed the ulcer to be 50 per cent smaller, which explained the subjective improvement. On April 29 the stoma could not be visualized, but the gastric mucosa "was normal in color instead of being fiery red as seen on the last visualization." May 6, after slightly over one month's therapy with sodium alkyl sulfate, the gastroscopic report was, "no ulceration was seen, there was no edema and acute inflammation had entirely left the stomach." On May 20 the gastroscopic report was, "no ulceration was seen, and the mucous membrane was apparently intact throughout. The rugal markings were a little more red than normal and apparently slightly edematous." Opinion: "A normal gastric stump with a moderate amount of acute superficial gastritis."

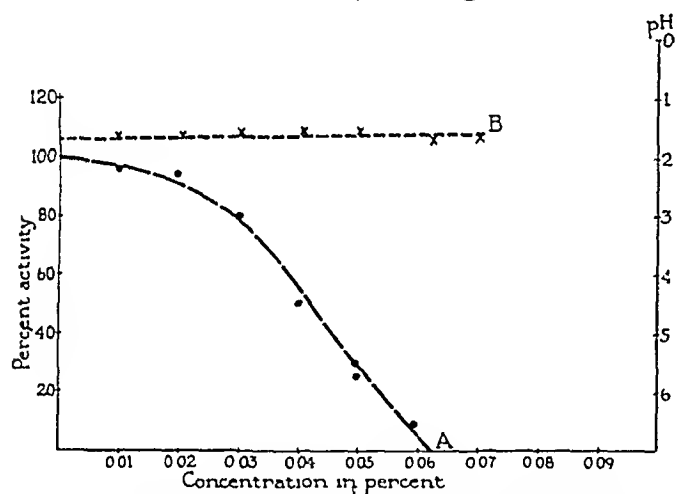


Chart 5—Sodium alkyl sulfate decreases peptic activity without any alteration in  $p_H$ . Note effectiveness of dilute concentrations. A represents activity of pepsin, B,  $p_H$ .

This patient was discharged May 22, 1942, well enough to leave a hospital or a convalescent home for the first time in two and one-half years. He immediately took a ten hour a day job in a foundry and despite warning stopped both medication and diet. By November he again had symptoms of ulcer which required hospitalization. Another marginal ulcer was visualized but responded to treatment with sodium alkyl sulfate. On March 8, 1943 this man was symptom free and self supporting.

CASE 29—A diagnosis of duodenal ulcer was made in 1931 in regard to a 49 year old man. He tried almost every known therapy for the ulcer without relief until 1941, when gastroenterostomy was done. This afforded no relief, and he was a patient either in the Northwestern University Medical School Clinic or the Wesley Memorial Hospital for one year. During this time varied orthodox routines were tried. He adhered faithfully to the prescribed regimens without relief. On June 6, 1942, gastroscopic examination demonstrated a lesser curvature, prepyloric and a gastrojejunal ulcer, each

about  $2\frac{1}{2}$  inches (6 cm) in diameter. The sodium alkyl sulfate routine was started, with marked diminution of subjective symptoms within four days. On June 30 gastroscopic study revealed almost complete healing of both ulcers. He was discharged from the hospital July 25. During his stay in the hospital the routine laboratory findings remained unchanged except the icteric index, which on June 25 was 12.5. Subsequently it returned to 5.3, where it remained.

November 9 he reentered the hospital, complaining of vomiting with complete absence of pain. November 10 the gastroscopic report indicated complete healing of the gastric and stomal lesions. A gastric resection was done then, and the pathologist's report was, "no break in the mucosa, some injection and some hemorrhage in the mucosa with perivascular and lymphatic infiltration."

These two large ulcers had healed, and they remained healed, despite obstruction, while the patient followed the sodium alkyl sulfate routine.

#### COMMENT

The role of pepsin in the formation of ulcer may now be reevaluated. Our studies have shown that the antacids customarily used clinically in the management of patients with ulcer inhibit peptic activity indirectly through change in gastric acidity. Dogs given daily injections of massive doses of histamine and fed sodium alkyl sulfate showed no change in gastric acidity, only inactivation of pepsin. These animals exhibited marked prolongation of survival time as contrasted with a similar series of animals not treated with sodium alkyl sulfate. In addition, healing was visualized by gastroscope in patients not responding to any other medication, including 2 patients who had undergone extensive gastric resections. Another patient, with an active gastrojejunal ulcer, was treated with sodium alkyl sulfate. He subsequently required gastric resection for obstruction. The resected specimen demonstrated histologic evidence of healing of the ulcer.

All this suggests reevaluation of the destructive factors in the genesis of ulcer.

From these studies, may we not consider the possibility that the satisfactory clinical results obtained with antacids have been achieved by indirect inactivation of pepsin through change of the hydrogen ion concentration rather than by neutralization of gastric acidity *per se*?

Acid is important. Without acid there is no ulcer. But without acid there is no peptic activity. The advantage of the routine suggested by us permits inhibition of peptic activity with a minimum of disturbance to body chemistry.

Research with surface-active agents has enabled us to separate the effect of peptic digestion from acid erosion. This has given encouraging results which will be further pursued in the attempt to clarify the enigma of ulcer and possibly afford a new and effective rationale of therapy for

ulcers that are resistant to orthodox management. At present, this clinical research is in its infancy. Further clinical experience has shown that the dosage may be safely increased two or three fold, although an occasional patient finds sodium alkyl sulfate irritating.

We are in complete accordance with Winkelstein,<sup>11</sup> who expects that "a new ulcer therapy should demonstrate (1) that it is rational, (2) that it is practical and (3) that it produces prompt and more persistent results than other forms of therapy." We add the stipulation, however, that a new form of ulcer therapy must heal ulcers which have not responded to the other types of therapy. The Abbott Laboratories are cooperating in supplying us with sufficient material so that sodium alkyl sulfate is being distributed to clinicians who will assist in its therapeutic evaluation. The product will be released to members of the medical profession only if it continues to demonstrate merit.

#### SUMMARY AND CONCLUSIONS

Sodium alkyl sulfate, a surface-active agent, was well tolerated by patients who were given 0.2 Gm. every two hours throughout the day.

<sup>11</sup> Winkelstein, A., Cornell, A., and Hollander, F. Intra-gastric Drip Therapy for Peptic Ulcer, *J. A. M. A.* 120:743 (Nov. 7) 1942.

No toxic effects occurred in either the experimental animal or man in the course of seven months' administration of this dose.

The survival time of dogs treated according to the Wangensteen technic with massive daily doses of histamine was markedly prolonged by the oral administration of sodium alkyl sulfate, which inactivated the pepsin in the stomach and did not alter the acidity.

All patients sent to us for clinical trial of sodium alkyl sulfate were classified as having "intractable" ulcer by their physicians because their symptoms could not be controlled by any orthodox management, including surgical therapy in 6. Twenty-six of 34 patients with gastroduodenal ulcerative disease had their symptoms controlled by sodium alkyl sulfate and were physically restored so that they were accepted by either the armed forces or industry.

Eight patients obtained no relief from this therapy. Two have already had recurrences on cessation of medication despite definite healing of the original lesions. Sodium alkyl sulfate is therefore not a panacea for all patients with ulcer. It does not cure the patient who is subject to ulcers but it will permit healing of some ulcers that are resistant to all other known types of management.

303 East Chicago Avenue

# PRIMARY ATYPICAL PNEUMONIA

AN ANALYSIS OF SEVEN HUNDRED AND THIRTYEIGHT CASES OCCURRING DURING  
1942 AT SCOTT FIELD, ILL.

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Primary atypical pneumonia as a clinical entity has only recently received prominent attention. It is usually a mild disease, differing widely from the classic lobar and bronchial pneumonias, it is communicable, has a prolonged period of incubation and is prone to occur in military camps, schools and other groups with frequent intimate contacts. It is a nonbacterial disease. It is characterized by insidious onset, coughing and progressive malaise, there is usually a brief febrile period during which the pulse and the respiration are relatively slow and there is a relative or absolute leukopenia, with minimal early signs of pneumonia but with the rales persisting after the roentgenogram appears normal.

There is little evidence that this is a new disease since reports of a similar pneumonia extend back into the nineteenth century. Stansfield,<sup>1</sup> in 1923, discussed the pulmonary involvement in 12 cases of grip. Cole and MacCallum,<sup>2</sup> summarizing data on pneumonias occurring in military camps in 1918, mentioned one type of bronchopneumonia with pathologic changes similar to those of primary atypical pneumonia. Leichtenstern,<sup>3</sup> reviewing the influenza epidemic of 1889, likewise commented on certain pneumonic complications unlike those in the majority of cases of influenzal pneumonia. Delafield,<sup>4</sup> in 1884, described a "rare" subacute bronchopneumonia of adults. Interstitial pneumonia has been detected in preserved lungs of soldiers of the Civil War, and pneumonia following measles in the War of 1812 has been mentioned.<sup>5</sup> All these in certain respects resemble the current form of atypical pneumonia.

However, the increasing occurrence of atypical pneumonia in the past few years cannot be attributed solely to increased recognition. In reports covering periods of several years, Bowen<sup>6</sup> in Hawaii, Miller and Hayes<sup>7</sup> at the University of Oregon, Smiley, Showacre, Lee and Ferris<sup>8</sup> at Cornell University, Murray<sup>9</sup> at Harvard University, McKinlay and Cowan<sup>10</sup> at the University of Minnesota, Gallagher<sup>11</sup> and Goodrich and Bradford<sup>12</sup> have described a steadily increasing incidence of this disease.

The majority of cases have been reported from military establishments. Bowen<sup>6</sup> in 1935 described 120 cases in the armed forces at Hawaii, and Allen<sup>13</sup> at Fort Sam Houston, Texas, gave impetus to its recognition. Over 1,750 cases have so far been reported from these military posts and from those in Louisiana,<sup>14</sup> Texas,<sup>15</sup>

6 Bowen, A. Acute Influenza Pneumonitis, *Am J Roentgenol* **34** 168-174 (Aug) 1935

7 Miller, F. N., and Hayes, M. G. Bronchopneumonia of Mild Severity at University of Oregon, *Northwest Med* **38** 12-14 (Jan) 1939

8 Smiley, D. F., Showacre, E. C., Lee, W. F., and Ferris, H. W. Acute Interstitial Pneumonitis. A New Disease Entity, *J A M A* **112** 1901-1904 (May 13) 1939

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11 Gallagher, J. R. Acute Pneumonitis. Report of an Epidemic, *Yale J Biol & Med* **13** 769-781 (July) 1941

12 Goodrich, B. E., and Bradford, H. A. The Recognition of Virus Type Pneumonia, *Am J M Sc* **204** 163-179 (Aug) 1942

13 Allen, W. H. Acute Pneumonitis, *Ann Int Med* **10** 441-446 (Oct) 1936

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15 Duggan, L. B., and Powers, W. L. An Acute Respiratory Infection Resembling So-Called Acute Pneumonitis, *U S Nav M Bull* **40** 651-659 (July) 1942

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2 Cole, R., and MacCallum, W. G. Pneumonia at a Base Hospital, *J A M A* **70** 1146-1156 (April 20) 1918

3 Leichtenstern, O. Influenza und Dengue, in Nothnagel, H. *Specielle Pathologie und Therapie*, Vienna, A. Holder, 1896, vol 4, pt 1, pp 1-222

4 Delafield, F. The Pathology of Broncho-Pneumonia, *Boston M & S J* **111** 484-487, 1884

5 Wall, J. S. Interstitial Bronchopneumonia in Children, *South M J* **30** 201-206 (Feb) 1937

Florida,<sup>16</sup> California,<sup>17</sup> Canada,<sup>18</sup> North Carolina<sup>19</sup> and Panama<sup>20</sup> Only 5 deaths have been mentioned, an incidence of 0.3 per cent

Studies of over 1,100 cases from civilian sources have been published Several of the early reports were from England<sup>21</sup>, in this country atypical pneumonia has been described in New York,<sup>22</sup> Massachusetts,<sup>23</sup> New Jersey,<sup>24</sup> Washington, D C,<sup>25</sup> Maryland,<sup>26</sup> Pennsylvania,<sup>27</sup> Virginia,<sup>28</sup> North Carolina,<sup>29</sup> Ohio,<sup>30</sup>

16 Green, D M, and Eldridge, F G Primary Atypical Pneumonia, Etiology Unknown, *Mil Surgeon* **91** 503-517 (Nov) 1942

17 Whitely, J H, Bernstein, A, and Goldman, M Primary Atypical Pneumonia—A Report of Twenty-Five Cases, *Mil Surgeon* **91** 499-502 (Nov) 1942

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23 (a) Gallagher, J R Bronchopneumonia in Adolescence, *Yale J Biol & Med* **7** 23-40 (Oct) 1934 (b) Cass, J W The Question of "Influenza" and Atypical Pneumonia, *New England J Med* **214** 187-193 (Jan 30) 1936 (c) Bock, A V Clinical Observations, Complications and Treatment of Acute Upper Respiratory Tract Infections, *Ann Int Med* **12** 317-322 (Sept) 1938 (d) Gallagher, J R Acute Pneumonitis A Report of Eighty-Seven Cases Among Adolescents, *Yale J Biol & Med* **13** 663-678 (May) 1941 (e) Favour, C B Ornithosis (Psittacosis) A Report of Three Cases and a Historical, Clinical, and Laboratory Comparison with Human Atypical (Virus) Pneumonia, *Am J M Sc* **205** 162-187 (Feb) 1943 (f) Murray<sup>9</sup> (g) Gallagher<sup>11</sup>

24 Raney, W G, and Burbridge, J R Acute Pneumonitis or Atypical Pneumonia, *Journal-Lancet* **59** 101-104 (March) 1939

25 Hornbrook, J W, and Nelson, K R An Institutional Outbreak of Pneumonitis I Epidemiological and Clinical Studies, *Pub Health Rep* **55** 1936-1944 (Oct 25) 1940

26 Longcope, W T (a) Bronchopneumonia of Unknown Etiology (Variety X) A Report of Thirty-Two Cases with Two Deaths, *Bull Johns Hopkins Hosp* **67** 268-305 (Oct) 1940, (b) Pneumonitis or Virus Pneumonia, *Practitioner* **148** 1-8 (Jan) 1942

27 (a) Reimann, H A An Acute Infection of the Respiratory Tract with Atypical Pneumonia, *J A*

Michigan,<sup>12</sup> Minnesota,<sup>31</sup> Illinois,<sup>32</sup> Oklahoma,<sup>33</sup> Texas,<sup>34</sup> California<sup>35</sup> and Oregon<sup>31c</sup> In general these cases seem to be more severe, with 26 deaths reported (2.4 per cent) This is not unexpected, as the patients with the milder attacks of the disease either are not seen by physicians or are treated at home

The nomenclature of this disease has become confused because of the uncertain etiology Etiologic terms such as "acute influenza pneumonitis,"<sup>6</sup> "influenzal pneumonitis"<sup>33</sup> and "primary virus pneumonitis"<sup>31c</sup> lack laboratory confirmation "Disseminated focal pneumonia"<sup>21b</sup> has been proposed on the basis of the roentgenographic appearance, "atypical pneumonia with leukopenia"<sup>34</sup> emphasizes a laboratory finding, "acute interstitial pneumonitis"<sup>8</sup> reflects the microscopic appearance Such terms as "pneumonitis" or "acute pneumonitis"<sup>13</sup> do not seem sufficiently limiting At present the most popular names indicate the uncertain etiology "atypical pneumonia,"<sup>23b</sup> "atypical bronchopneumonia,"<sup>9</sup> "bronchopneumonia of unknown etiology,"<sup>30</sup> or the official military diagnosis,

*M A* **111** 2377-2384 (Dec. 24) 1938 (b) Reimann, H A, and Havens, W P An Epidemic Disease of the Respiratory Tract, *Arch Int Med* **65** 138-150 (Jan) 1940

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36 Longcope<sup>26a</sup> Kneeland and Smetana<sup>22a</sup>

"primary atypical pneumonia, etiology unknown" <sup>37</sup>

In 1942, at the Station Hospital, Scott Field, 799 patients were treated for pneumonia. Twenty-four had typical lobar pneumonia, 775, bronchopneumonia. Among the latter were 738 patients with clinical and laboratory find-

TABLE 1—*Types of Onset of Atypical Pneumonia (Seven Hundred and One Cases)*

	Cases
Asymptomatic onset. Patients admitted because routine roentgen films revealed pulmonary cloudiness	6
Onset with cough	247
Cough, gradual development of malaise, finally fever	214
Cough and pleuritic pain	20
Cough without other symptoms	13
Abrupt onset	260
Sudden malaise and coughing	175
Malaise initially, cough soon following	55
Malaise initially, cough late if at all	30
Onset with coryzal symptoms	122
Miscellaneous	66
Predominant symptom	
Sore throat, mild pharyngeal injection	32
Sore throat, acute follicular tonsillitis	8
Laryngitis	9
Malaise following typhoid vaccinations	9
Nausea, vomiting and/or diarrhea	8

ings suggestive of a nonbacterial cause. The remaining 37 patients suffered from the more widely recognized types of primary or secondary bacterial bronchopneumonia. The atypical pneumonia varied from that observed in a few critically ill patients to the milder forms which seemed no more serious than the ordinary "cold." Hospitalization varied from a few days to several months, and there was a distinct seasonal variation. Yet clinically this whole group exhibited sufficiently uniform signs and symptoms to be classed together as having primary atypical pneumonia.

#### CLINICAL FINDINGS IN THE SEVEN HUNDRED AND THIRTY EIGHT CASES OCCURRING IN 1942

*Type of Onset*—The explosive onset of pneumococcal lobar pneumonia was rarely seen in the atypical disease. A characteristic history (table 1) was as follows. There had been bouts of coughing for several days, the patient began to feel tired and weak, there was intermittent chilliness, as well as fever and diaphoresis. True rigors were not present in any of these cases. Early the cough was nonproductive, the paroxysms often occurred following a change in position, especially during the night and on awakening in the morning. Pleuritic pain was rare, but substernal aching with coughing or deep breathing was almost the rule.

On the other hand, symptoms at times developed rapidly, though rarely in less than one to two days. In these cases malaise, aching, chilliness and fever heralded the illness, with cough following in from one to four days. In 1 patient cough was never present. Hence the diagnosis was occasionally established prior to the presence of pulmonary symptoms.

The third large group of patients had symptoms indistinguishable from those of coryza: sneezing, nasal discharge, pharyngeal irritation with associated cough and mild discomfort.

Analysis of the types of onset showed a definite seasonal variation (table 2). During the summer months the onset was more abrupt and as a rule the course was milder, requiring shorter hospitalization. During the winter the gradual onset with cough or mild coryzal symptoms predominated.

*Interval Between Admission to Hospital and Diagnosis of Pneumonia*—Early findings in atypical pneumonia were usually not prominent but were sufficiently clear to enable the diagnosis to be made within the first twenty-four hours in 57 per cent of the cases, however, 9 per cent were not correctly diagnosed within the first week. In certain cases pneumonia was suspected for the first time when an apparently simple respiratory infection did not subside rapidly. In others it was masked by conditions such as asthma or measles. Further, there was always the question of cross infection in the wards.

*Findings in Chest*—The most consistent single finding was moist rales. However, other changes

TABLE 2—*Monthly Variation in Incidence of Types of Onset of Atypical Pneumonia*

1942	Abrupt Onset	Cough	Coryza
January	10	14	3
February	7	6	6
March	6	13	5
April	15	23	3
May	6	10	3
June	15	15	5
July	46	33	0
August	38	26	17
September	35	14	16
October	39	29	20
November	25	27	20
December	18	37	15

alone or in combination were often present (table 3). In almost half the cases the chest revealed nothing unusual on admission examination, but in all but 49 it did subsequently disclose physical findings (table 4).

The rales usually heard early in atypical pneumonia were fine "sticky" crepitations, occurring in showers at the end of fairly deep inspirations and accentuated by coughing. As the disease

<sup>37</sup> Primary Atypical Pneumonia, Etiology Unknown, editorial, War Med 2 330-333 (March) 1942.

progressed, the rales became louder and coarser and were heard during a greater portion of the inspiratory phase and later during the complete respiratory cycle. It was during this stage that dulness, diminished breath sounds and decreased fremitus were sometimes evident. At times the coarse rales faded promptly, but often they per-

TABLE 3—Thoracic Findings on Admission to Hospital (Seven Hundred and Thirty-Four Cases)

	Cases	Per Cent
Chest clear	327	45
Moist rales	274	37
Rough breath sounds	64	8.7
Rhronchi	39	5.2
Dulness	20	2.7
Friction rub	8	1.1
Increased breath sounds	2	0.3

sisted after the roentgenographic changes had disappeared and the patient was well along in his convalescence. At times the rales changed to a variety of rhonchi before disappearing. Dingle and his associates<sup>14b</sup> have graphed the relationship of the chest findings to the roentgen appearance, indicating that the roentgenogram detects pneumonic changes earlier and clears more rapidly than is suggested by the clinical findings. Duggan and Powers<sup>15</sup> also emphasized the persistence of rales.

When pulmonary disease was apparent, the involved lobe or lobes were usually readily identified. Rales heard posteriorly suggested lesions of the lower lobe and those heard anteriorly lesions of the upper lobe. When no signs in the chest were noted, the patient occasionally indicated the site of involvement by complaints of "fulness" or "aching" in one side of his chest.

TABLE 4—Summary of All Thoracic Evidences of Disease Observed During Hospitalization (Seven Hundred and Thirty-Four Cases)

	Cases	Per Cent
Moist rales	548	75
Fine	469	64
Coarse	160	22
Roughened breath sounds	191	26
Dulness	163	22
Rhronchi	103	14
Bronchial breathing	52	7.1
Diminished fremitus	32	4.4
Friction rub	13	1.8
Flatness (without effusion)	5	0.7
Whispered pectoriloquy	4	0.6
No findings	49	6.7

Also, there was often a history of increased discomfort or uncontrollable coughing when lying on the affected side.

*Relation of Findings in Chest to Severity of Illness*—One of the most atypical features of this pneumonia was the complete dissociation between the findings in the chest and the extent of the patient's symptoms, disability, fever and

other complaints or between either of these factors and the roentgenographic appearance of pulmonary cloudiness. There might be an apparently clear chest, very slight haziness on the roentgen film, yet an acutely ill patient. On the other hand, loud rales may have been heard widely on the roentgenogram may have shown patchy cloudiness throughout a lobe while the patient was only slightly uncomfortable. This was particularly true in cases in which roentgenograms never revealed definite pneumonia, yet the clinical course was indistinguishable from that of atypical pneumonia.

CLINICAL COURSE OF ATYPICAL PNEUMONIA

*Illness Prior to Hospitalization*—Symptoms usually preceded the admission of the patient to the hospital by one to seven days, occasionally weeks when a chronic cough would not "break."

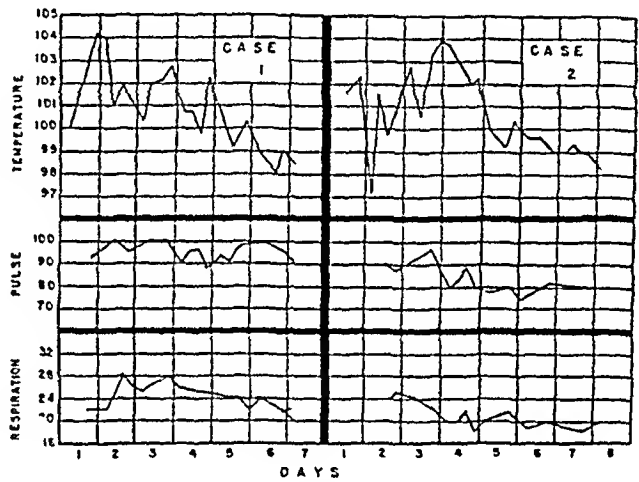


Fig 1—The usual febrile course as seen in 2 patients with atypical pneumonia. The pulse and respiratory rates are relatively low.

That acute symptoms of weakness, aching and fever infrequently persisted over twenty-four hours is indicated in the fact that the intensive schooling the men received demanded full mental and physical faculties. The length of the illness prior to hospitalization in the winter (six to eight days) was practically double that of mid-summer (three to five).

*Duration of Illness*—The average period of hospitalization was twenty-seven days, varying from twenty in summer to twenty-nine in early winter. Of this total, patients were acutely ill an average of only three and four-tenths days (two and one-tenth days in summer, four and nine-tenths days in winter).

*Fever*—In atypical pneumonia, unlike the common infections of the respiratory tract fever was seldom at the peak on admission but frequently was at the peak within the first forty-



eight hours. Temperatures ranged from normal throughout hospitalization to 106.6 F. The average peak for all cases was 102.8 F. The duration of temperatures over 100 F averaged five days, that of temperatures over 99 F seven and five-tenths days (figs 1 and 2).

Patients with high fever were quite uncomfortable, especially if there was associated uncontrollable coughing. However, there was no comparison between a patient having atypical pneumonia with a temperature of 104 F and a similar patient with lobar pneumonia. The former appeared flushed and ill at ease but in no acute distress, occasionally sitting up in bed to read or converse (fig 3). Reimann<sup>27a</sup> has mentioned a biphasic type of fever, suggestive of virus infection, but it was not characteristic in this series.

hospitalization, was noted in 84 cases (12 per cent). The bronchoscopic findings of inflamed readily injured mucosa by Dingle and co-workers<sup>14b</sup> and the pathologic findings of ulcerated bronchial mucosa explain this tussive blood-streaking.

*Sore Throat, Pain*—The pharynx was often quite injected but seldom actually red as in exudative pharyngitis. However, Green and Eldridge<sup>16</sup> stated that red, congested, swollen throats were almost invariably present, and Reimann and Havens<sup>27b</sup> noted that 92 per cent of their series had inflamed mucous membranes.

The characteristic dry and hacking cough often caused a "raw throat", "burning" tracheitis, marked substernal aching, pain along the ribs margins, pain and occasionally tenderness with slight rigidity of the abdominal muscles, usually

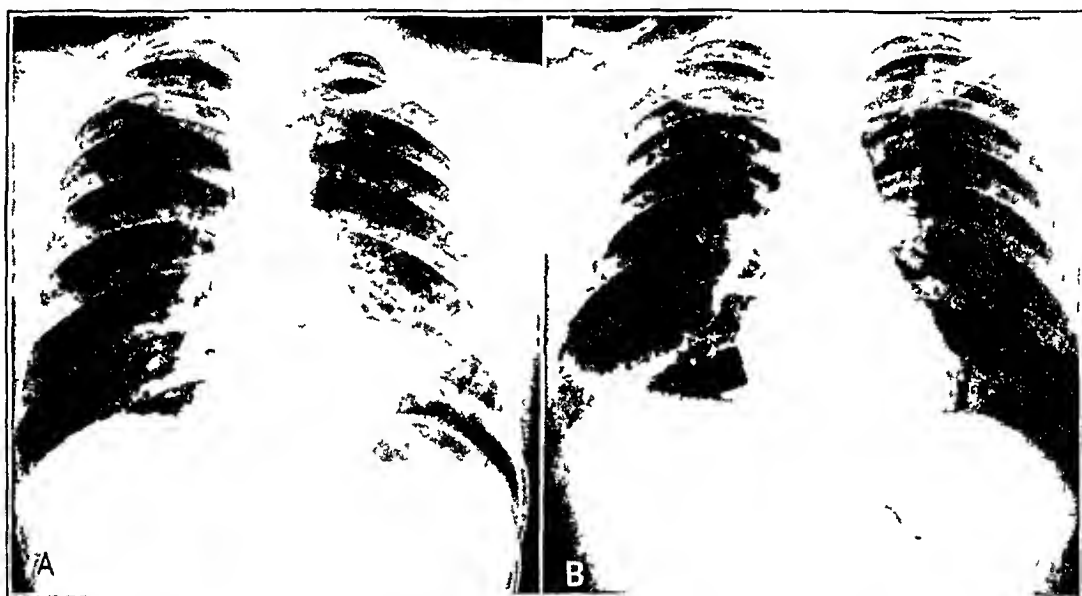


Fig 2—A, roentgenogram of the chest in case 1 on the second hospital day. This illustrates the classic cloudy mottling projecting from the hilar region.

B, roentgenogram of the chest in case 2 on the second hospital day. An unusual form of atypical pneumonia with accentuation of the bronchovascular markings extending into the right costophrenic angle.

*Pulse and Respiratory Rates*—The pulse and the respiration were typhoidal. The pulse was full but not rapid, the respiration, deepened but not accelerated. The pulse rate was usually a more accurate guide than the temperature to the extent of pulmonary disease, as a rising pulse rate suggested spreading pneumonia (fig 4), and a slow pulse in the face of a high, persistent fever indicated little cause for alarm. Seriously ill patients with rapid respiration were usually benefited by oxygen even though cyanosis and dyspnea were absent.

*Hemoptysis*—In 2 cases there was copious hemoptysis of bright red blood. In neither was the cause detected, and there was complete subsidence of bleeding as the disease regressed. Blood-streaked sputum, either before or during

in the epigastric region, pain along the pelvic attachments of the abdominal musculature. In 1 patient this pain in the lower part of the abdomen was interpreted as appendicitis, however, the appendix and other abdominal viscera appeared normal at operation. Green and Eldridge<sup>16</sup> have also reported a case in which appendectomy was performed because of the pain in the lower part of the abdomen.

*Splenic Enlargement*—Longcope<sup>26a</sup> noted that 12 per cent of his patients had splenomegaly, however, in the present series no splenic or hepatic enlargements were detected.

*Convalescence*—There was no sharp demarcation between the acute and the convalescent stage of atypical pneumonia as typified by the crisis of pneumococcic pneumonia. Rather, the

fever slowly diminished, and the cough which had been nonproductive began to "loosen" with production of tenacious clear phlegm. There remained, however, a period of debility which was difficult to explain solely on the basis of pulmonary disease. For weeks and even months the patient had little energy, tired easily and had insufficient appetite to regain the weight lost during the early stage. This probably accounts for the longer hospitalization of patients in army camps than in civilian life, as discharge from a

*Relation of Age to Course of Illness*—Patients ranged in age from 17 to 46. Within these limits there was no definite relation of age to severity or length of illness.

#### LABORATORY FINDINGS

*Roentgenologic Examination*—The roentgenogram is the most important aid in the diagnosis of atypical pneumonia, as it may establish early the presence and the extent of the pulmonary lesion. However, it is not the sole means of

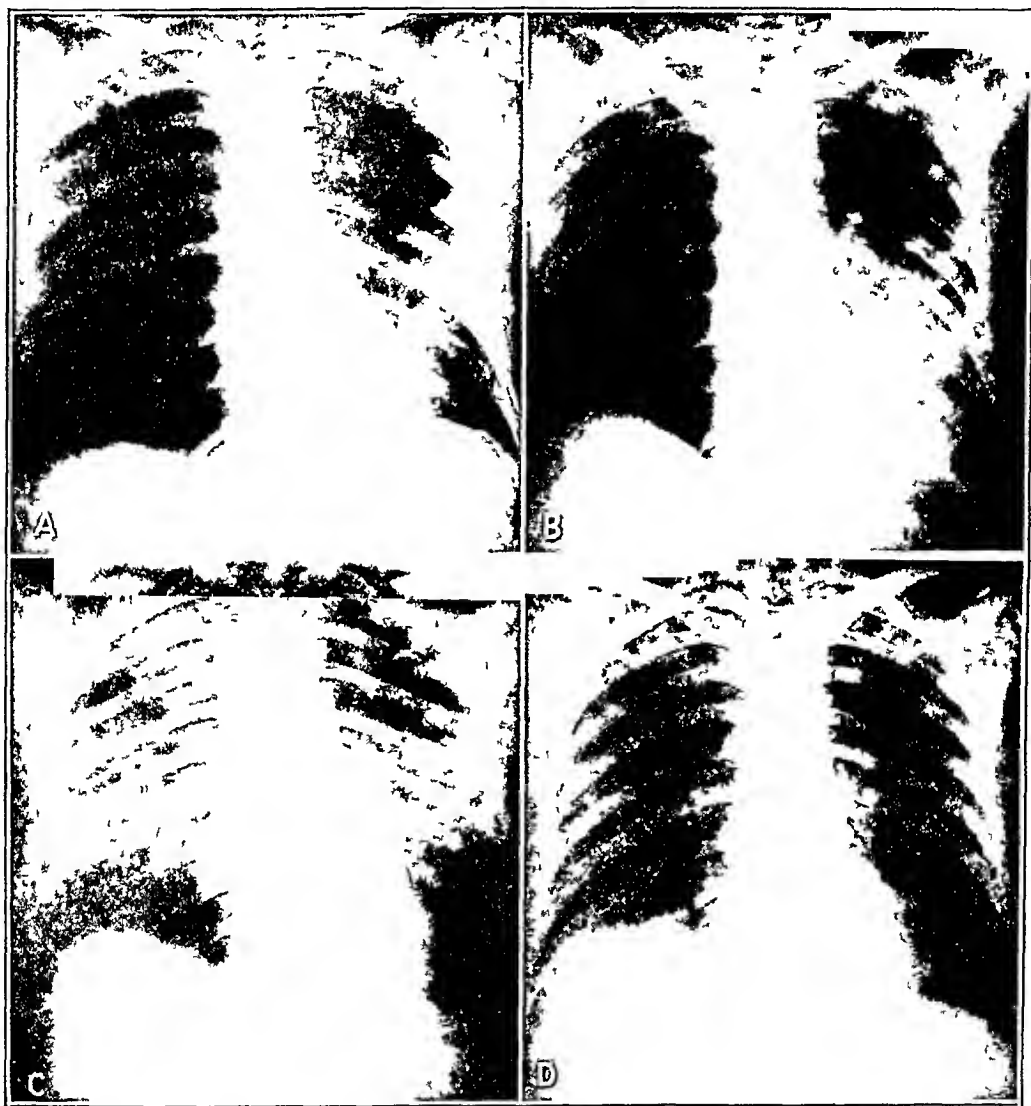


Fig 3 (case 3)—*A*, roentgenogram of the chest taken when the patient was admitted to the hospital. Note the patchy areas of consolidation in the midportion of the lower lobe of the left lung.

*B*, roentgenogram of the chest on the fourth day. There is confluent mottling throughout the lower lobe and the lower portion of the upper lobe of the left lung.

*C*, roentgenogram of the chest on the twelfth day. All lobes are at least partially involved with the consolidations of atypical pneumonia.

*D*, roentgenogram of the chest on the eighteenth day. Only traces of the pneumonia remain.

station hospital means return to active duty. If too energetic activity was resumed prematurely, the patient at best had a mild reactivation of coughing and development of fever, a more serious consequence was an exacerbation of his pneumonia. Frequently coughing was the last symptom to disappear.

diagnosis, an altogether too prevalent belief. For example, Duggan and Powers<sup>15</sup> stated that "in a large majority of cases [diagnosis] could not be made by any other means."

Roentgenograms taken early reveal accentuation of the hilar bronchovascular markings on one or both sides. Hazy densities project out-

ward toward the periphery of the lungs, having at first a mottled appearance, at times progressing to a more uniform cloudiness. The process may involve small portions of one lobe or may cover one or more lobes completely. With spread of the pneumonia there is again an extension from the hilar regions. Regression is not an absolute

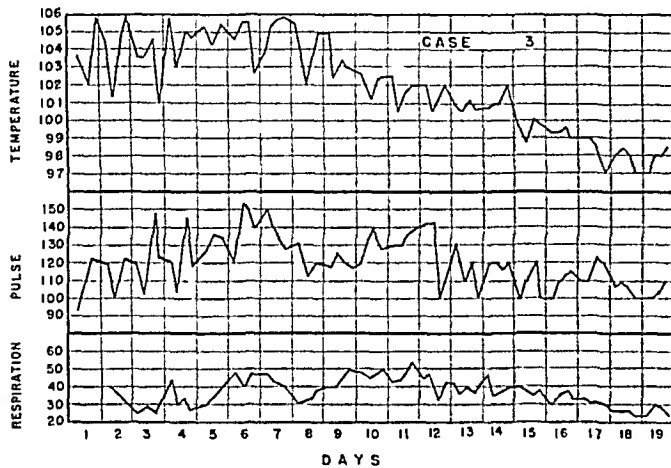


Fig 4 (case 3)—A critically ill patient with a temperature of 105 F for eight days. However, the pulse and respiratory rates indicate the pneumonic changes more precisely than does the temperature. Figure 3 reveals that there was steadily increasing consolidation during the first twelve days.

reversal, as the entire pneumonic area begins to fade at once, although the intensification of the bronchovascular markings is usually the last to subside. Occasionally an area of consolidation seems to enlarge slightly as its density begins to diminish.

The average duration of pulmonary consolidations in uncomplicated cases was nineteen days, as determined by serial roentgen films taken usually at seven day intervals.

Classifications of roentgenograms<sup>38</sup> stress the various stages of the disease, e. g., accentuation of hilar markings with projections toward the periphery, which McCarthy<sup>14c</sup> found to be most common, or patchy confluent areas of density, or generalized increase in pulmonary markings. The most characteristic picture is that of uneven densities, or cloudy mottling, as seen in figures 1 A and 3 A and B. An unusual type is characterized by peripheral areas of consolidation, sometimes suggestive of early lobar pneumonia, as in figure 2 B.

A predilection for involvement of a lower lobe was marked, occurring in 612 cases (83 per cent), with a slight but definite predominance of the left lower lobe (table 5). Extensions of

the pneumonic process occurred in 64 cases, with extension to the opposite lung in 40.

The diagnosis of pneumonia was made in 15 cases (2 per cent) with no definite roentgen changes beyond accentuation of truncal markings, this seemed justified from the clinical course and findings. Dingle and his associates<sup>14b</sup> have also noted the difficulty in distinguishing between certain types of tracheobronchitis and tracheobronchopneumonia.

In 30 cases (4 per cent) the findings in the chest suggested pneumonia while the initial roentgen films appeared normal, though the later ones were confirmatory. The detection of pulmonary signs prior to roentgenographic evidence is in sharp contrast to the usual minimal findings in the early stages. In 14 cases, in which both the roentgen and the thoracic findings were negative early but subsequently positive, pneumonia was suspected on the basis of the history and the general appearance of the patient.

*Studies of Sputum*—Certain roentgen films suggested a tuberculous process. Sputums from 52 patients were studied for *Mycobacterium tuberculosis*. In no instance were acid-fast organisms discovered.

Sputums from 275 patients were examined for the presence of *Diplococcus pneumoniae*. Gram-positive diplococci were found in 82 sputums, but in only 28 were type-specific pneumococci identified. Types usually considered to be

TABLE 5—Lobes Involved in Atypical Pneumonia as Determined by Roentgenography

	Cases
Involvement of a single lobe throughout illness	577
Left lung	217
Right lung	200
Lower lobe of left lung	289 (50%)
Lower lobe of right lung	208 (36%)
Upper lobe of right lung	32 (5.5%)
Upper lobe of left lung	28 (5.0%)
Middle lobe of right lung	20 (3.5%)
Involvement of more than one lobe on admission to the hospital	78
Lower lobes of right and left lungs	37 (47%)
Middle and lower lobes of right lung	10 (13%)
Entire left lung	9 (12%)
Entire right lung	6 (8%)
All lobes of both lungs	4 (5%)
Other combinations	12 (15%)

significant were present in sputums from 6 patients: 1, 2, 5, 7, 9 and 11. The majority of the remaining types found were the less significant higher types. In no case were the identified organisms etiologically important from a clinical standpoint. Certain of the cases ruled out of this series were cases of bronchopneumonia with type-specific pneumococci, marked leukocytosis, tachycardia and response to chemotherapy.

<sup>38</sup> Kornblum, K., and Reimann, H. A. The Roentgenological Aspects of an Epidemic of Acute Respiratory Tract Infection, *Am J Roentgenol* 44:333-344 (Sept) 1940. Smiley, Showacre, Lee and Ferris<sup>8</sup> McCarthy<sup>14c</sup>

*Blood Counts*—A relative leukopenia with respect to fever and severity of illness was characteristic. The average leukocyte count on admission was 9,860, although the mean value, 9,080, was more representative. The lowest count was 2,600, the highest, 30,000. The summer leukocyte counts averaged distinctly lower (9,200) than the winter ones (10,250). These figures tend to confirm the majority of reports, although Cass<sup>23b</sup> stated that in his series most leukocyte counts ranged from 2,500 to 4,500 (80 to 90 per cent polymorphonuclear cells), with the lower counts representing the more seriously ill patients.

Differential counts were made in only a few cases. They showed that fluctuation varied with the polymorphonuclear leukocytes and that in counts under 8,000 there were often eosinophils up to not more than 10 per cent. Longcope<sup>26a</sup> noted slight eosinophilia in over half of his 32 cases. However, this disease does not apparently simulate Löffler's eosinophilic pneumonia.<sup>39</sup>

Among patients who were critically ill, counts of 15,000 to 18,000 were common, uninfluenced by treatment with sulfonamide compounds. With convalescence the leukocytosis usually dropped parallel with clinical improvement, while low counts tended to rise to normal or slightly higher. Kneeland and Smetana<sup>22a</sup> and Curtzweiler and Moore<sup>19</sup> found moderate leukocytosis with convalescence in even the milder illnesses.

Erythrocyte counts were normal, although during convalescence hemoglobin values were often slightly depressed.

*Urinalysis*—Urinalysis was performed routinely, yet in only 8 cases were abnormalities detected. Glycosuria occurred in 2 cases early in the illness and disappeared promptly. Albuminuria was observed in 4 instances, in each case at the height of the fever, and lasted from one to four days. None of the patients with these symptoms was seriously ill. Following the use of sulfonamide compounds, transient hematuria was detected in 2 patients.

*Blood Cultures*—In the few instances in which blood cultures were made they were negative. This confirms the observations of Reimann<sup>27a</sup> and of Daniels.<sup>28</sup>

*Serologic Tests*—The Kahn test was performed in 518 cases. In 3 cases it was transiently positive (0.6 per cent), in only 1 case was it positive as long as four weeks. Kneeland and Smetana<sup>22a</sup> reported a similar case.

39 Reimann, H. A. Infectious Diseases, Arch Int Med 64 362-405 (Aug) 1939.

## PATHOLOGY

No patients with uncomplicated atypical pneumonia died. Four patients were extremely sick, and though death was felt to be imminent, all recovered. One patient, admitted with a diagnosis of atypical pneumonia, died of empyema with the additional observation at autopsy of typical bacterial bronchopneumonia, so that the case was excluded from this series.

Golden<sup>40</sup> has given an excellent summary of the pathologic observations in "primary interstitial pneumonia." In the uncomplicated cases there are diffuse whitish peribronchial nodules. The bronchioles are filled with gross pus consisting of cellular debris and polymorphonuclear leukocytes. However, the cellular infiltration of the peribronchial tissue is essentially free of polymorphonuclear cells, with lymphocytes, plasma cells and monocytes extending into adjacent alveolar walls. Congestion and edema of the lung tissue are common, again free of polymorphonuclear leukocytes and bacteria. With secondary infection, hemorrhage, polymorphonuclear leukocytes and fibrin formation become prominent but do not obscure the fundamental process. Other organs commonly show alterations: the spleen, congestion but not hyperplasia; the liver, minute foci of necrosis; the diaphragm, hyaline necrosis of muscle fibers. Golden stated that these pulmonary lesions are not pathognomonic of atypical pneumonia, as similar changes are found in other interstitial pneumonias of known causes.

Thirty-one deaths from atypical pneumonia have been reported, including 9 in the severe epidemic among infants reported by Adams and his associates.<sup>41</sup> The remaining 22 deaths occurred in 7 patients who apparently were overcome by the severity of the pneumonia<sup>42</sup> and who had pleurisy<sup>22a</sup> and sterile effusions<sup>43</sup>, 2 with empyema caused by *Streptococcus haemolyticus* infection<sup>23b</sup>, 1 who succumbed to intercurrent lobar pneumonia<sup>21d</sup>, 2 who had fatal encephalitic complications<sup>44</sup>, 5 who had cardiac disabilities, 3 who had old rheumatic carditis<sup>45</sup>, 1 in whom autopsy re-

40 Golden, A. Interstitial Pneumonitis, Army Medical Museum Study Material, January 1943.

41 Adams<sup>31b</sup> Adams, Green, Evans and Beach<sup>31c</sup>

42 Lillie, R. D., Perrin, T. L., and Armstrong, C. An Institutional Outbreak of Pneumonitis. III. Histopathology in Man and Rhesus Monkeys in the Pneumonitis Due to the Virus of "Q" Fever, Pub Health Rep 56 149-155 (Jan 24) 1941. Eaton, Beck and Pearson<sup>35a</sup> Moore, Tannenbaum and Smaha<sup>14a</sup> Hufford and Applebaum<sup>30</sup>

43 Reimann<sup>27a</sup> Green and Eldridge<sup>16</sup>

44 Reimann<sup>27a</sup> Scadding<sup>21b</sup>

45 Longcope<sup>26a</sup> Moore, Tannenbaum and Smaha<sup>14a</sup>

vealed myocarditis<sup>32</sup>, 1, a 79 year old patient, whose heart failed<sup>21d</sup>. There were pathologic reports on most of these cases, and the findings uniformly included peribronchial interstitial pneumonia. Saphir, describing postmortem observations on 2 patients, mentioned, in addition, hyaline membranes lining the pulmonary alveoli and intracytoplasmic inclusions of the bronchial epithelium<sup>46</sup>.

#### TREATMENT

No specific therapy is known for atypical pneumonia, so that treatment is entirely symptomatic. For general malaise in the present series of cases codeine seemed most efficient. Acetyl salicylic acid alone or in combination with acetophenetidin and caffeine effected prompt falls in temperature as a rule and thereby tended to relieve the generalized aching associated with fever. However, the accompanying drenching sweat was uncomfortable, and the erratic temperature curve made estimation of progress uncertain. As a result, routine use of the antipyretic drugs was discouraged. Sponge baths and alcohol rubs had a soothing as well as antipyretic effect.

Most troublesome to the patient and most difficult to control was coughing. During the early nonproductive stage no expectorant was found adequate. Codeine and various cough mixtures were routinely employed, with transient benefit at best. Proprietary cough drops, slowly dissolved in the mouth, at times reduced the "tickling" in the throat. With paroxysmic coughing benefit was occasionally obtained from "steam" inhalations.

If cyanosis or dyspnea developed, the use of an oxygen tent was of unquestioned value. Cyanosis, which was infrequent in this series, was found by Rhoads<sup>32</sup> in 12 of his 24 patients.

Convalescent serum or blood was not used, and blood transfusions were given in only the critical cases, so that benefit was difficult to determine. Green and Eldridge<sup>16</sup> noted suggestively beneficial results from the use of convalescent blood in 2 patients.

During convalescence, non-ultraviolet rays or sunbaths, deep-breathing and graduated physical exercises were apparently helpful.

*Chemotherapy*—Sulfonamide drugs were employed in 362 cases, with a sharp break in temperature following their administration in 42 (12 per cent), suggesting a favorable response. However, since the febrile period was usually brief, it was often difficult to determine whether

a fall in temperature would not have occurred anyway.

Sulfanilamide was used in 73 cases, with apparent benefit in 8 per cent, sulfapyridine, in 21 cases, with no response, sulfathiazole, in 300 cases, with a seeming response in 11 per cent, and sulfadiazine in 61 cases, with abrupt improvement in 10 per cent. More than one type of the drug was used for the occasional patient. The dosage of the sulfonamide compound was almost invariably 4 Gm initially, followed by 1 Gm every four hours, sodium bicarbonate was occasionally added. Sulfapyridine was the most unpopular, inducing nausea and vomiting routinely. Sulfadiazine was best tolerated but only slightly more so than sulfathiazole.

The incidence of apparent response to sulfonamide compounds (12 per cent) in patients with leukocytosis on admission was no greater.

TABLE 6—*Relationship of Leukocytosis to the Response to Sulfonamide Compounds*

Leukocyte Count on Admission	Patients Not Receiving Sulfonamide Compounds	Patients Receiving Sulfonamide Compounds	
		Total	Number in Whom Chemo-therapy Was Apparently Effective
12,000 to 14,950	47	50	4
15,000 to 17,950	17	22	4
18,000 to 19,950	4	8	2
20,000 and over	3	11	1
Totals	71	91	11 (12%)

than the incidence of apparent response in all patients receiving sulfonamide compounds (table 6). This suggests that the elevated counts did not represent secondary bacterial invasion but actually reflected the primary pathologic process.

The use of sulfonamide compounds was generally discredited, but in any patient who was severely ill or whose disease was protracted full doses were employed in an attempt to prevent or eradicate secondary infection. Statistics which seem to show a more rapid recovery in patients not treated with sulfonamide compounds<sup>17</sup> must be subjected to careful scrutiny inasmuch as only the patients with more severe disease are usually given chemotherapy.

*Other Types of Therapy*—Uhlman mentioned "dramatic effects" from the use of roentgen radiation to the chest<sup>47</sup>. Goodrich and Bradford<sup>12</sup> injected neoarsphenamine into 3 patients without benefit. Campbell<sup>20</sup> in the treatment of patients

46 Saphir, O. Pathological Changes in So-Called Atypical Pneumonia, *Radiology* 40 339-343 (April) 1943.

47 Uhlman, E, in Discussion of Symposium on Atypical Pneumonia, *Radiology* 40 360-361 (April) 1943.

for malaria and atypical pneumonia found the latter unaffected by quinine

#### RECURRENCES

Seventeen patients with recurrent atypical pneumonia were admitted to the hospital during 1942, 2 of them for a third time. Recurrences are infrequently mentioned in the literature, for example, in Gallagher's<sup>11</sup> series of 87 cases seen over a seven year period there were no recurrences.

The interval between the initial disease and the recurrence varied from one to one hundred and twenty-three days, with the number of cases insufficient to establish a reliable average (mean, eighteen days). Usually the recurrent pneumonia was less severe, to judge by the duration of fever over 100 F—four and four-tenths days as compared with five and eight-tenths days originally. This was not necessarily true in the individual case, as one of the most critically ill patients was one with recurrent pneumonia.

Ten patients had reinfection of the same pulmonary lobe, while the other 7 had recurrences in areas partially or totally different from those involved in the primary disease. In all these the chest had been clear to physical examination on initial discharge from the hospital. However, in 7 instances the final roentgen film did not show complete resolution. This suggests a more conservative management of patients in whom the disease may seem to have cleared clinically but not roentgenographically.

#### COMPLICATIONS

**Lungs**—Thirty patients (4 per cent) exhibited roentgen evidence of pleurisy, usually as cloudiness of the costophrenic angle. In only 15 was there clinical evidence of fluid. Thoracentesis was performed on 4, and the fluid was uniformly clear and sterile except that of 1 patient with empyema. In this patient, in whom the onset was characteristically that of atypical pneumonia, fever began subsiding on nonspecific therapy shortly after admission. A sudden rise in temperature was associated with a reddened throat, from which the beta hemolytic streptococcus was isolated. Evidence of effusion became apparent, and culture of the fluid revealed the same organism. Purulent empyema developed with leukocytosis. Several months later this patient was still critically ill.

Hospitalization of patients with effusion was uniformly prolonged. An average of nineteen days was recorded for those whose condition was uncomplicated, in 1 instance, however, the patient was in the hospital for six months. Six

cases of pleural effusion with 1 death<sup>48</sup> and 4 cases of empyema with 2 deaths<sup>49</sup> are described in the literature. One case of pulmonary abscess was described by Bowen.<sup>6</sup> There have been no cases of secondary staphylococcal pneumonia at Scott Field, such as Finland, Strauss and Peterson<sup>50</sup> described in an epidemic of an influenza-like disease in December 1940 and January 1941.

Atelectasis developed in the middle and lower lobes of the right lung of 1 patient with atypical pneumonia of the entire right lung. The course was relatively severe, with fever over 100 F persisting for twelve days. However, recovery was complete in twenty-seven days.

**Alimentary Tract**—Irritation of the alimentary tract was evidenced by pronounced nausea and vomiting (4 cases), diarrhea (8) or both (4) with little relief from atropine and bismuth, the stools revealed no pathogenic organisms. Symptoms usually subsided within one or two days but in 1 instance lasted ten days. Many patients were nauseated, apparently from gagging during paroxysms of coughing, sedation was usually effective. Reimann and Havens,<sup>27b</sup> discussing 400 patients with pneumonia and associated respiratory diseases, mentioned marked gastrointestinal upsets in 4 and catarrhal jaundice in 3.

**Skin**—Herpes about the lips and the face was noted in 6 cases (1 per cent). Healing was prompt in those receiving sodium iodide intravenously. Dermatitis following the administration of sulfonamide compounds occurred in 2 cases.

**Genitourinary Tract**—Four patients with albuminuria and 2 with glycosuria have been mentioned. Pronounced burning and smarting on urination developed in 2 patients (aged 23 and 30) with no urinary changes or findings of organic changes in the urinary tract. No specific treatment was given, and the symptoms subsided completely in two and five days.

**Nervous System**—Neurologic complications occurred in 1 patient, aged 22, whose history of cough dated back one week.

The day before admission he noticed soreness and weakness in both legs. On the second hospital day he was unable to use his lower extremities, and reflexes of the ankles, the knees and the cremaster and abdominal muscles were absent, the patient remained alert. The third day his arms became weak, on the

48 Reimann<sup>27a</sup> Maxwell<sup>21d</sup> Green and Eldridge<sup>16</sup> Goodrich and Bradford<sup>12</sup>

49 Cass<sup>23b</sup> Maxwell<sup>21d</sup> Adams<sup>31b</sup>

50 Finland, M., Strauss, E., and Peterson, O. L. Staphylococcal Pneumonia Occurring During an Epidemic of Clinical Influenza, *Tr. A. Am. Physicians* 56: 139-146, 1941.



fifth day the upper lip felt numb, and by the sixth day the right side of the face was paralyzed, with weakness of the left side of the face and absence of taste noted. Generalized weakness of the body, predominantly of the left side, progressed. The seventh day the patient was inarticulate and drowsy, he thrashed about his bed when uncontrolled by sedation. From this day on he slowly recovered. By the fourteenth day strength in the extremities was almost normal, but a month later facial palsy was still present. Laboratory tests all gave normal values except for spinal fluid protein. On the fourth day the finding was 142 mg per hundred cubic centimeters, on the seventh, 326 mg, on the twenty-third, 112 mg, on the thirty-fifth the value given by the Pandy test was reported as normal. The pneumonia was mild with the temperature never exceeding 100 F, and recovery was uneventful. Attempts to implicate the viruses of lymphocytic choriomeningitis, influenza, lymphogranuloma venereum, and meningo-pneumonitis failed.

In most reports of large series of cases mention is made of neurologic complications. In 5 cases meningismus has been described,<sup>51</sup> with no deaths, and in 4 encephalitis,<sup>52</sup> with 1 death.

*Other Tissues*—Otitis media complicated 3 cases of atypical pneumonia, erysipelas and purulent conjunctivitis, 1 each. In all instances there was a response to sulfonamide compounds, and apparently the complication did not hinder pneumonic resolution.

#### ATYPICAL PNEUMONIA AS A COMPLICATION

Atypical pneumonia developed postoperatively in 7 patients and during the puerperium of 2. Diagnostic differentiation from the more characteristic postoperative bacterial pneumonias was not difficult as a rule. The combination of atypical pneumonia and asthma, bronchiectasis or hay fever occurred in 5 patients, all of whom had marked respiratory distress. In 1 patient convalescing from scarlet fever, atypical pneumonia developed without evidence of streptococcal complications. In 2 patients with measles pneumonia developed with pulmonic infiltrations more extensive than described by Kohn and Koiransky<sup>53</sup> as occurring in uncomplicated measles. One case of combined malaria and pneumonia occurred, such as has been described by Campbell.<sup>20</sup>

Atypical pneumonia may be a serious complication of heart disease, as 5 fatalities have been reported. In the Goodrich and Bradford<sup>12</sup> series of 52 patients, gallop rhythm developed in 6, with electrocardiographic changes in 3. Green and Eldridge<sup>16</sup> noted that one third of

their series showed mild tachycardia during convalescence and 3 transient cardiac enlargement. In 3 patients with cardiac disease (congenital rheumatic and chronic myocarditis respectively) in this series pneumonia developed, but in none did the heart become decompensated or show other evidence of progressive cardiac injury.

#### DIFFERENTIAL DIAGNOSIS

Most of the pneumonic patients were sent to the hospital with a diagnosis of nasopharyngitis or bronchitis, and distinguishing the pneumonia from these infections of the upper respiratory tract was the primary problem. With auscultatory findings in the chest the problem was usually not difficult. In the remainder, unusual malaise, persistent nonproductive cough or protracted illness without obvious cause warranted roentgenographic examination of the chest. Certain types of bronchitis were difficult to distinguish from atypical pneumonia.

Once the diagnosis of pneumonia was made, the relative bradycardia, the leukopenia and the type of thoracic findings distinguished the atypical form from the pneumonias caused by bacterial infection. Technical laboratory methods are required to rule out the known virus and rickettsial pneumonias which closely simulate (and may include) this atypical disease.

Tuberculosis was suggested by the hazy, mottled roentgen appearance, especially when the disease occurred in the upper lobes, and by the frequency of blood-streaked sputum. The clinical illness, the sputum negative for acid-fast organisms and the rapidly clearing roentgenograms tended to rule out tuberculosis. On the other hand, the findings in initial roentgen films were occasionally interpreted as pneumonia, but because of the stability of the lesions, tuberculosis was eventually diagnosed.

No coccidiosis was observed in this series, but from the description of Dickson and Gifford<sup>54</sup> it would be difficult to rule out clinically, especially if the characteristic erythematous nodules in the skin were absent. Kneeland and Smetana<sup>22a</sup> described a patient with an erythematous eruption of the skin, and Maikham<sup>18</sup> mentioned a patient with erythema multiforme without discussing the differentiation from coccidiosis.

#### EPIDEMIOLOGY

*Predisposing Factors*—A study of the predisposing factors has not revealed any significant clues other than those commonly attributed to

51 Hornbrook and Nelson<sup>25</sup> Kneeland and Smetana<sup>22a</sup> Markham<sup>18</sup>

52 Reimann<sup>27a</sup> Scadding<sup>21b</sup> Green and Eldridge<sup>16</sup>

53 Kohn, J. L., and Koiransky, H. Successive Roentgenograms of the Chest of Children During Measles, *Am J Dis Child* **38** 258-270 (Aug) 1929

54 Dickson, E. C., and Gifford, M. A. Coccidioides Infections (Coccidioidomycosis) II The Primary Type of Infection, *Arch Int Med* **62** 853-871 (Nov) 1938



the simple infections of the upper respiratory tract. Many have a history of onset of symptoms with climatic change, fatigue or loss of sleep, most were unable to explain the onset. If atypical pneumonia is caused by a psittacine virus, as is suspected by some, it is of interest that fowl contract ornithosis (psittacosis) much more readily if they occupy congested cages<sup>55</sup> or if they receive insufficient thiamine in the diet<sup>56</sup>.

Twenty-seven patients had been recently hospitalized with simple infections of the respiratory tract, at intervals of one day to three weeks, with the greatest concentration at two weeks. In those with one or two day intervals the diagnosis was probably unsuspected during the first hospitalization. The same statement might apply to the patients with the extended intervals, some may have been exposed to pneumonia during the initial illness, and certainly in a few the development of atypical pneumonia was a coincidence.

Eleven patients with apparently mild infections of the respiratory tract suddenly had marked aching and malaise after typhoid vaccinations, and were found to have pneumonia. Compared with the total number of soldiers receiving the vaccinations, this was a negligible incidence.

*Incubation Period*—In an army camp, where there are multiple contacts, it is difficult to ascertain the one through which disease may have been transmitted. Study of the spread of pneumonia through the barracks revealed little as to the incubation period, for example, one barrack had 1 case one week, 2 the next, then none for four weeks. Few barracks had no recognized cases, yet no one barrack had over 8 throughout the year. The literature is almost unanimous with respect to an incubation of one to three weeks, most likely about two. Hufford and Applebaum<sup>30</sup> discussed a case with an apparent incubation of four days, and intimations of even shorter periods have been made.

Of 124 patients whose length of station at Scott Field was sought, 60 contracted pneumonia within four weeks, 43 in five to eight weeks, 15 in nine to twelve weeks and 4 in thirteen to sixteen weeks, the greatest concentration occurred at the end of the first week. As at all army posts, there is a constantly changing population at Scott Field. Gallagher<sup>11</sup> has sug-

gested this as a factor, he noticed that the occurrences in his school community were highest among newcomers.

*Contagiousness*—The small number of soldiers who contracted atypical pneumonia as compared with the characteristic rapid overwhelming spread of influenza or even of measles and scarlet fever among those susceptible suggests low contagiousness. There was no indication during 1942 of significant increase or decrease in the contagiousity or severity of atypical pneumonia.

In the medical group, 8 enlisted men, 4 nurses, 3 doctors and 2 dentists contracted the disease, an incidence considerably less than for the whole field, unlike the high incidence reported by Dingle and associates<sup>14b</sup>. Eaton, Beck and Pearson<sup>35a</sup> and Moss<sup>20</sup> have described severe forms which were unusually contagious. The suggestion of Smiley, Showacre, Lee and Feiris<sup>8</sup> and of Moore, Tannenbaum and Smalia<sup>14a</sup> that such measures as ward isolation and wearing of masks be carried out would be applicable in such cases but seems to have little place in military camps, where the disease is generally mild, where there has been widespread exposure before diagnosis is established and where apparently the rate of contagion is low.

One veterinarian was hospitalized with atypical pneumonia, he revealed that a number of animals, notably dogs, were being treated by the Veterinary Corps for a type of pneumonia which in many respects simulated that of human patients. No studies were made to see if there was any etiologic connection.

*Seasonal Variations*—During 1942 there were two peaks of cases of simple infection of the respiratory tract (rhinitis, pharyngitis, tonsillitis, laryngitis, tracheitis, bronchitis) one in mid-February and one early in December, the low point occurred late in August. On the other hand, the cases of pneumonia averaged about 4 per 10,000 of population per week until June then climbed rapidly during July to 10 to 15 per 10,000 per week. A secondary rise and the greatest single monthly concentration occurred during October (fig 5). During the early months of 1943 a steady decline to early 1942 levels has become apparent. In the series of Dingle and his co-workers<sup>14b</sup> also the peak occurred during the summer. However, the majority of reports suggest that the seasonal peak occurs in the fall and early part of winter. Markham<sup>18</sup> feels that most cases are seen in the winter and spring.

In addition to the variations of incidence there were distinct clinical variations with change of

55 Meyer, K. F., Eddie, B., and Yanamura, H. Y. Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, *Proc Soc Exper Biol & Med* **49** 609-615 (April) 1942.

56 Pinkerton, H., and Swank, R. L. Recovery of Virus Morphologically Identical with Psittacosis from Thiamin-Deficient Pigeons, *Proc Soc Exper Biol & Med* **45** 704-706 (Nov) 1940.

season. Prehospital days of illness were fewer during the summer than during the winter. Onset during the summer was not only shorter but more abrupt and was characterized initially by malaise rather than by coughing. The duration of the acute stage of illness in the hospital showed three phases. During June and July it was four to six days, from August to October it was two days on an average, and during the early winter it increased again to three to five days. Hospitalization averaged twenty days during the summer and twenty-nine days during the winter. Leukocyte counts were distinctly lower during the summer (9,200) than during the winter (10,250). Thus, the summer pneumonia was milder with more sudden onset, a brief acute stage and rapid convalescence.

*Mode of Spread Through Camp* (fig 6) — The field is divided into segregated "areas" within which the soldiers are assigned to training schools. In one area, where the schools border a semicircle, the July wave of pneumonia struck each school in definite progression, with one to two weeks between their peaks. In another area the schools border a rectangle, and again the sequential progression was evident. Spread through the latter area was more rapid than through the former, and a contributing factor may have been the greater congestion.

#### ETIOLOGY

Etiologic studies have been directed primarily at the exudates from the respiratory tract. Pneu-

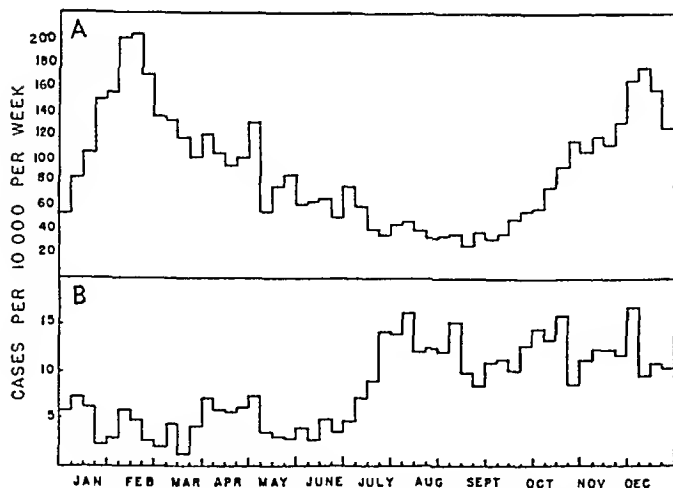


Fig 5—The incidence of atypical pneumonia (lower curve) compared with that of infections of the upper respiratory tract (upper curve) in 1942.

cocci were uncommonly present and were chiefly of the higher types. *Streptococcus viridans* was consistently isolated, but no great significance is usually attached to it. Rhoads,<sup>32</sup> however, on the basis of studies of mice feels it may be important.

In most reported cases studies for viruses have failed completely to show any, but the exceptions are outstanding.<sup>57</sup>

*Psittacosis Virus* — Eaton, Beck and Pearson<sup>33a</sup> isolated the virus of psittacosis from 4 cases of severe atypical pneumonia (2 fatal) and successfully transmitted it to mice, hamsters and

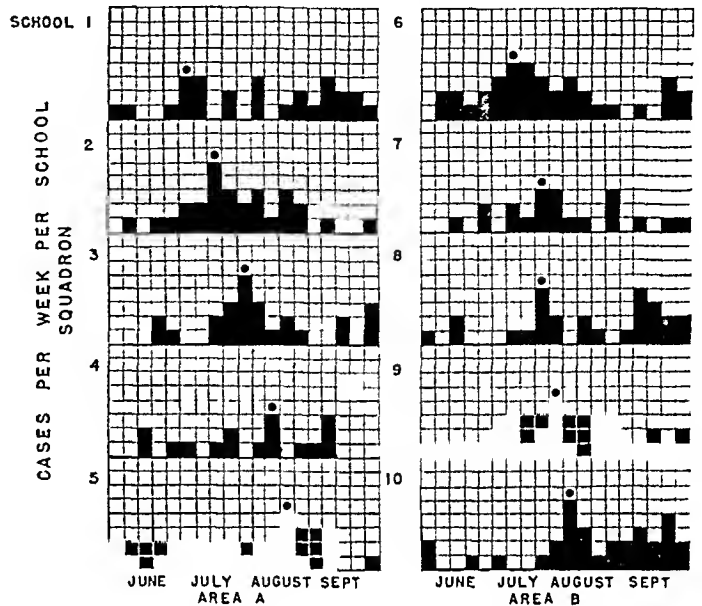


Fig 6—Progression of atypical pneumonia through five schools in each of two "areas" on Scott Field. Dots accentuate the progressing peaks in the schools.

guinea pigs. This virus was found to be closely related to the virus of meningopneumonitis isolated by Francis and Magill<sup>58</sup> from influenza-like cases in the 1934 and 1936 epidemics. In 4 Negroes with atypical pneumonia Dingle's group<sup>14b</sup> found unchanging high levels of complement-fixing antibodies for the virus of meningopneumonitis. Stickney and Heilman<sup>59</sup> identified the agent from one rather seriously ill patient as the psittacine virus. Meyer, Eddie and Yanamura,<sup>55</sup> Favour<sup>23e</sup> and Reimann, Havens and Price<sup>60</sup> found this virus responsible for sev-

57 Virus pneumonias, including atypical pneumonia are completely summarized by Finland, M., and Dingle, J. H. *Virus Pneumonias, I Pneumonias Associated with Known Nonbacterial Agents*. Influenza, Psittacosis and Q Fever, *New England J Med* **227** 342-350 (Aug 27) 1942. Dingle, J. H., and Finland, M. *Virus Pneumonias, II Primary Atypical Pneumonias of Unknown Etiology*, *ibid* **227** 378-385 (Sept 3) 1942.

58 Francis, T., Jr., and Magill, T. P. *An Unidentified Virus Producing Acute Meningitis and Pneumonitis in Experimental Animals*, *J Exper Med* **68** 147-160 (Aug) 1938.

59 Stickney, J. M., and Heilman, F. R. *The Isolation of a Virus in Atypical Pneumonia*, *Proc Staff Meet, Mayo Clin* **17** 369-375 (June 17) 1942.

60 Reimann, H. A., Havens, W. P., and Price, A. H. *Etiology of Atypical ("Virus") Pneumonias with a Brief Resume of Recent Experiences*, *Arch Int Med* **70** 513-522 (Oct) 1942.

eral cases of atypical pneumonia, as determined by complement-fixation tests Favou<sup>23c</sup> has clearly shown the clinical relationship of atypical pneumonia and ornithosis (psittacosis) Baker<sup>61</sup> recognized an atypical pneumonia in cats which was apparently contagious for man and vice versa The agent was transmissible from cats to mice and chick embryos, in which were recognized elementary bodies similar to those of psittacosis

Dr Thomas Francis Jr, at the University of Michigan, performed agglutination tests on serum from 23 patients at Scott Field In all cases blood was drawn as soon as the diagnosis was established, and in 12 instances further blood was drawn one month later The highest titer was 1:8, in 1 case Of the remaining 34 tests, 4 gave a titer of 1:4, 9 a titer of 1:2 and 21 a titer of 0 Influenzal serologic tests were reported negative by Dr Francis, which is in agreement with the literature

*Rickettsia of Q Fever*—Dyer, Topping and Bengston<sup>62</sup> were able to isolate this etiologic agent from 3 of 4 patients in an isolated outbreak of atypical pneumonia<sup>25</sup> Hesdorffer and Duffalo<sup>63</sup> mentioned 1 case of mild pneumonia in which infection with *Rickettsia diaphana* was indicated by serum agglutination titers of 1:80 and 1:160 However, Green and Eldridge<sup>16</sup> reported no evidence of infection with this rickettsia in 15 patients

*Virus of Lymphogranuloma Venereum*—The Frei test was found to be positive in 5 of 8 patients by Rake, Eaton and Shaffer<sup>64</sup> My associates and I have performed the test on 23 patients, using chick embryo antigen (*Lygiatum*), with negative results Dingle and associates<sup>14b</sup> found negative reactions in 7 patients Eaton, Martin and Beck<sup>30b</sup> have demonstrated the antigenic relationship of the viruses of lymphogranuloma venereum and meningopneumonitis

61 Baker, J A A Virus Obtained from a Pneumonia of Cats and Its Possible Relation to the Cause of Atypical Pneumonia in Man, *Science* **96** 475-476 (Nov 20) 1942

62 Dyer, R E, Topping, N H, and Bengston, I A An Institutional Outbreak of Pneumonitis II Isolation and Identification of Causative Agent, *Pub Health Rep* **55** 1945-1954 (Oct 25) 1940

63 Hesdorffer, M B, and Duffalo, J A American Q Fever, *J A M A* **116** 1901-1902 (April 26) 1941

64 Rake, G, Eaton, M D, and Shaffer, M F Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis, and Lymphogranuloma Venereum, *Proc Soc Exper Biol & Med* **48** 528-531 (Nov) 1941

*Viruses Not Previously Recognized*—Reimann,<sup>27a</sup> Reimann and Havens<sup>27b</sup> and Stokes, Kenney and Shaw<sup>65</sup> were able to produce pneumonia in ferrets by inoculating these animals with washings from the noses and throats of patients with atypical pneumonia The viruses became attenuated or were lost in passage

Weir and Horsfall<sup>66</sup> were able to produce pneumonia in wild mongooses with washings from the throats of 4 patients (types of illness not described) The causative virus was filtered through Berkefeld V and N candles, was not inactivated by glycerin, by freezing or by drying in vacuo, and was propagated on the chorio-allantoic membranes of chick embryos

Eaton, Meikeljohn, Vantterick and Talbot<sup>67</sup> transmitted a virus to cotton rats with sputums from 17 of 18 patients who had atypical pneumonia This virus was filtered through Berkefeld N candles in 2 of 6 instances It was not transmissible to common laboratory animals

Adams, Green, Evans and Beach<sup>31c</sup> studied a severe form of pneumonia in young infants No virus was found, but intracytoplasmic inclusion bodies were detected in pulmonary epithelial cells and in cells in smears of material obtained from throats

Viruses are apparently inherent in certain animals (mice<sup>68</sup> and hamsters<sup>69</sup>), and serial passages may increase their virulence to the point of producing pneumonia This should be taken into consideration in etiologic studies of atypical pneumonia

65 Stokes, J, Jr, Kenney, A S, and Shaw, D R A New Filtrable Agent Associated with Respiratory Infections, *Tr & Stud, Coll Physicians, Philadelphia* **6** 329-333, 1939

66 Weir, J M, and Horsfall, F L The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose, *J Exper Med* **72** 595-610 (Nov) 1940

67 Eaton, M D, Meikeljohn, G, Vantterick, W, and Talbot, J C An Infectious Agent from Cases of Atypical Pneumonia of Unknown Etiology Apparently Transmissible to Cotton Rats, *Science* **96** 518-519 (Dec 4) 1942

68 Dochez, A R, Mills, K C, and Mulliken, B A Virus Disease of Swiss Mice Transmissible by Intranasal Inoculation, *Proc Soc Exper Biol & Med* **36** 683-686 (June) 1937 Gordon, F B, Freeman, G, and Clampitt, J M A Pneumonia-Producing Filtrable Agent from Stock Mice, *ibid* **39** 450-453 (Dec) 1938 Horsfall, F L, and Hahn, R G A Pneumonia Virus of Swiss Mice, *ibid* **40** 684-686 (April) 1939 Nigg, C An Unidentified Virus Which Produces Pneumonia and Systemic Infection in Mice, *Science* **95** 49-50 (Jan 9) 1942

69 Pearson, H E and Eaton, M D A Virus Pneumonia of Syrian Hamsters, *Proc Soc Exper Biol & Med* **45** 677-679 (Nov) 1940

## SUMMARY

Seven hundred and thirty-eight cases of atypical pneumonia were recognized during 1942 at the Station Hospital, Scott Field, Ill. Serious complications were rare, there were no fatalities. The disease showed epidemic tendencies during the late summer and fall when common diseases of the respiratory tract were at a minimum. Seasonal clinical variations were apparent.

Atypical pneumonia attacks congregated groups of people, especially young adults. The degree of contagion and the recoverability of the etiologic agent seem to vary with the severity of the illness. After an incubation period of one to three weeks, there develops in the exposed person a nonproductive cough, accompanied or followed by fever, aching, weakness and loss of

appetite. Cough is the most troublesome symptom but tends to be relieved within a few days as the fever diminishes by lysis. The pulse rate, the respiratory rate and the leukocyte count are little elevated in uncomplicated cases, and there is a lack of such clearcut findings as are observed with pneumococcal pneumonia. Prolonged convalescence is the rule, and if a patient is seen for the first time during convalescence, neurocirculatory asthenia may be suggested. Complications are uncommon, but the occasional development of effusion and empyema warrants recognition of the primary disease. From a military standpoint the time lost is significant. Over 20,000 man-days (or 55 man-years) were lost at Scott Field during 1942 from atypical pneumonia.

# HODGKIN'S DISEASE—INCIDENCE AND PROGNOSIS

## A STATISTICAL CORRELATION WITH THE CLINICOPATHOLOGIC PICTURE

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WASHINGTON, D C

At the conclusion of his article on Hodgkin's disease in the 1939 University of Wisconsin Symposium on Blood, Krumbhaar<sup>1</sup> succinctly commented "Thus we see that in general, the problems of Hodgkin's disease in the past generation remain the problems of today. We still do not know whether it is an infectious granuloma or a neoplasm, and, therefore, we are ignorant of its pathogenesis, we have no specific laboratory diagnostic test other than the biopsy examination. We have no means of predicting how long a given case will survive, and we have no specific form of treatment."

It was with the hope of throwing some light on the two last-named factors that this study was undertaken. The review also included a careful search for clues as to a common predisposing factor or etiologic agent. However, the main question posed was: Are there any criteria for predicting the course and duration of the disease?

A cursory review of any series of cases of Hodgkin's disease immediately suggests the desirability of a biopsy study. When the first few cases were analyzed it became apparent that a restudy of the biopsy slides is not just a

a restudy of all the biopsy and autopsy material with attention to the minute details is a *sine qua non*.

### MATERIAL

The clinical histories of 244 cases were analyzed. These represent the cases of all the patients with Hodgkin's disease who were admitted to the Edward Hines Hospital during the eleven years, from 1930 to 1940, inclusive. Eight patients had no biopsies. The 5 dead patients had an average total duration of the disease of 51 months. Of the 3 patients still alive, 1 had it for 156 months, another for 132 months and the third for 36 months. One can thus readily see what havoc in the statistics of a small series of cases can be produced by the inclusion of cases without biopsy confirmation.

At the conclusion of the study it was found necessary to eliminate 11 more cases, 4 because of incomplete data and the other 7 because the diagnosis of Hodgkin's disease had been made erroneously. Enumeration of the corrected diagnoses is instructive, in that it shows with what entities Hodgkin's disease may be confused. The following are the corrected diagnoses: reticulum cell sarcoma, 2 cases, and chronic lymphadenitis, fungous infection, lymphoepithelioma, lymphosarcoma and benign lymphoma, 1 case each. (The condition in the last case defies more specific classification than as benign lymphoma.)

Two hundred and twenty-five cases of verified Hodgkin's disease were thus left in which microscopic studies had been made. On the basis of a restudy of the slides from 186 cases, inclusive of 67 autopsies, the following clinicopathologic classification was arrived at:

- |  |   |
|--|---|
| 1 Hodgkin's lymphoreticuloma { Typical<br>2 Hodgkin's granuloma { Atypical | { 1 Generalized                                     |
| 3 Hodgkin's lymphoma { Typical<br>{ Atypical                               | { 2 Superficial multiple glandular<br>{ 3 Localized |

desideratum but a necessity. The variations in the manifestations and severity of the disease must, a priori, be at least partially reflected in the pathologic picture. Soon 2 biopsy descriptions were encountered reading "cellular Hodgkin's disease", 1 patient was dead, having had a total duration of twelve months, and the other was alive, with a total duration of two hundred and thirty-six months. It then became clear that

From the Tumor Service, Veterans Administration Facility, Hines, Ill.

Published with the permission of the Medical Director of the Veterans Administration, who assumes no responsibility for the opinion expressed or the conclusions drawn by the author.

<sup>1</sup> Krumbhaar, E. B. The Present Status of Hodgkin's Disease, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, pp. 148-166.

### NOMENCLATURE

#### *A Histologic Definitions*

1 **Hodgkin's Lymphoreticuloma** This type has a prevalence of reticulum cells or frequent mitoses or both. Large or medium-sized lymphocytes when associated with frequent mitoses have a significance analogous to the reticulum cells, hence the inclusion of "lympho" in the term lymphoreticuloma.

2 **Hodgkin's Granuloma** This type, which occurred in the majority of the cases, shows the typical features of pleomorphism, Sternberg-Reed cells and a moderate degree of fibrosis.

3 **Hodgkin's Lymphoma** This type shows destruction of glandular architecture and only a slight tendency to pleomorphism, with a moderate persistence or prevalence of the lympho-

cytic element Most of the lymphocytes are of the small variety Some medium-sized lymphocytes may be present, but without any associated frequent mitoses It is with this type that occasionally one may have to make the diagnosis of Hodgkin's disease in the absence of Reed or Sternberg cells One must be sure, however, to segregate cases in which the diagnosis is so made in any statistical study with classification into typical and atypical forms The word typical would refer mainly to the important element of Sternberg-Reed cells

*B Clinical Stages*—From a clinical standpoint one recognizes three stages or degrees of involvement the localized, the superficial multiple glandular and the generalized The pathologic and clinical observations were therefore analyzed separately for these three stages or phases of involvement

#### ANALYSIS

*A Reference Point for Evaluation of Duration*—Several authors had already previously pointed out, and more recently Slaughter and Craver again emphasized the point, that one does not obtain a true picture of Hodgkin's disease by taking a single reference period for evaluation of duration of the disease There is an inherent fallacy in counting duration from the time of biopsy or of beginning of treatment This fallacy lies in the great variation in the period elapsed between the onset of the disease and the time the patient presents himself to the physician or institution where a biopsy is made or a definitive form of treatment is resorted to In favor of this reference point is the fact that the time of biopsy or of beginning of treatment is definitely known and is a matter of record This reliability is contrastedly lacking in the data as to onset obtained from the patient They are especially vague in cases in which the first manifestations are not glandular enlargement but systemic complaints, such as weakness, loss of weight, fever and osseous pain The duration after the patient's admission to the hospital, taken by itself, has little significance Some patients have had previous hospitalizations at other institutions and in fact may have had several courses of irradiation

In view of the aforementioned considerations, it was decided to represent each case by four numerical values in the form of two fractions, thus —

$$\frac{\text{Postnodal Duration}}{\text{Postbiopsy Duration}}, \quad \frac{\text{Existence of Nodes Prior to Definitive Treatment}}{\text{Total Duration After Onset of Symptoms}}$$

The first numerator stands for the total duration in months after the onset of glandular enlarge-

ment The first denominator denotes the number of months elapsed between the biopsy or the beginning of treatment and death or the last follow-up of those patients who are still alive The second numerator expresses the number of months that known glandular enlargements have existed prior to institution of definitive therapy The second denominator is used to denote the total duration of symptoms in those cases in which the first manifestation was cutaneous involvement or a systemic complaint

*B Correlation of Duration with Histologic Picture*—1 Generalized Lesions When the histologic picture is viewed as a whole one can readily divide the cases into instances of typical Hodgkin's disease and cases in which the condition for one reason or another is atypical In the latter, sections may fail to exhibit the important typical element, the Reed cell, and they usually present a prevalence of cells of the lymphocytic or reticuloendothelial series When this gross pathologic yardstick was applied, 96 (42.7 per cent) patients with typical generalized disease were found These had an average duration of 29.2/19.2, 16.8/31.3 Six of the 96 patients are still alive One has a total duration of 75 months and another of 50 months The remaining 4 thus far have an average duration of only 24 months

Of the 29 patients with an atypical generalized form of Hodgkin's disease, 12 formed a distinct group Their lesions were characterized by prevalence of reticulum cells and/or frequent mitoses These were not reticulum cell sarcomas but atypical Hodgkin's lymphoreticulomas In table 1 the clinical course of this subgroup is graphically compared with that of the remainder of the group with an atypical generalized form (Hodgkin's lymphoma) This segregated subgroup (with atypical Hodgkin's lymphoreticuloma) had a duration of 8.6/4.2, 5.2/9.6, as contrasted to a duration of 61.0/49.7, 29.0/64.7 for the remainder of the patients with atypical disease (atypical Hodgkin's lymphoma)

A similar subgroup with lesions exhibiting prevalence of reticulum cells and/or frequent mitoses (typical Hodgkin's lymphoreticuloma) was segregated from the 96 patients with a typical generalized form Seventeen such patients had an 18.7 month total duration, as against 34.9 months for the remainder of the group, and a duration of 10 months after the beginning of treatment, contrasted to 21.1 months for the remainder of the group It is to be noted that the total duration for the patients with typical generalized Hodgkin's disease with prevalence of reticulum cells and/or mitoses is about twice as much as the period for the groups with a



similar atypical form (187 as against 96 months) Evidently it takes time for some pleomorphism and Reed cells to develop The lesions which are more malignant never have a chance to acquire these characteristic features to any degree of prominence

2 Superficial Lesions The same major pathologic criterion of typicality applied to the 55

TABLE 1—Average Life Expectancy of Patients with Hodgkin's Disease After a Biopsy Which Reveals Typical Sternberg-Reed Cells

	Prevalence of Reticulum Cells	Fibrosis	Number of Cases	Average Duration in Months After Biopsy
Generalized	+		21	87
	—	+		173
	—	—		222
	— and also minus prevalence of medium lymphs	+		281
	Total		66	124
Superficial	+		9	110
	—	—	11	126
	—	+	12	285
	—	+	10	302
	—	+ and intact capsule	8	356
Localized	+		2	410, 780 →
	Total		25	210
	+	+	9	276
	—	—		537
	Total		22	390
Thirteen cervical				434
Three axillary				516
Two retroperitoneal				355
Four inguinal				150

cases with only superficial multiple glandular involvement yielded 31 with a typical histologic picture Twenty-six of these had an average duration of 481/360, 282/500 Three of the patients are alive, 1 with a duration of 68 months, 2 with duration of 33 months each

In 5 cases with typical changes there were the additional features of prevalence of reticuloendothelial cells and/or mitoses In these the disease had a much shorter course, averaging 10 months after biopsy and a total of 21 months after the appearance of nodes In the cases of the analogous atypical form (4) the duration was 8 and 122 months respectively This, again, is consistent with the conclusion that frequent mitoses associated with prevalence of reticuloendothelial cells and lacking in Reed cells and pleomorphism spell a short course A striking contrast was presented by the 11 remaining cases of atypical superficial Hodgkin's disease These had an average of 676 and 864 months post-biopsy and postnodal duration, respectively Five of the 11 patients are alive, with an average total duration of 159 months One of the 5 has adenopathy and is in poor condition The other 4

have small residual lymph nodes and are in good general condition

3 Localized Lesions The 28 patients who had localized cervical or axillary adenopathy exhibited a much more favorable course The average duration was 966/531, 467/973 In table 6 the cases of localized cervical Hodgkin granuloma are graphically contrasted to those of localized inguinal Hodgkin granuloma A rather surprising observation was the fact that the typical localized inguinal Hodgkin granuloma showed the least favorable course among the localized group of lesions One is tempted to suggest that inguinal involvement signifies wide dissemination

C Correlation of Duration with Individual Cellular and Stromal Components of the Biopsy Sections—1 Sternberg-Reed Cells Given a biopsy specimen with typical Sternberg-Reed cells, what is the patient's life expectancy? The important factors of mitosis, fibrosis and prevalence of reticulum cells were evaluated independently and in combinations The duration after biopsy is listed in table 1

The hyperchromatic Sternberg cells failed to show any differential prognostic value when compared with the vesicular Reed cells Similarly the giant cells of the Sternberg-Reed type, which were encountered in approximately half of the cases, and the finding of Reed cells lying in empty spaces did not show any added significance other than that of the usual Sternberg-Reed variety

2 Reticuloendothelial Cells Statistical evaluation of prevalence or predominance of reticuloendothelial cells as a single factor was impossible, since almost all these patients had mitoses Table 2 enumerates the duration for each of the three clinical phases of involvement Only 1 example each of localized, superficial and generalized

TABLE 2—Duration of Hodgkin's Disease Exhibiting Prevalence of Vesicular Variety of Reticulum Cells

	Number of Cases	Average Duration After Appearance of Nodes	Average Duration After Biopsy
Generalized	11	112	56
Superficial	5	412	122
Local	2	510	350
		230	40

lesions without mitosis were found with the vesicular reticulum cell variety Also 2 patients had superficial lesions without mitosis of the punctate reticuloendothelial variety These 2 patients lived only three months after biopsy The observations in these few cases—though not statistically significant—seem to indicate that the prevalence or predominance of reticuloendothelial cells by itself produces a short course for the



patients with superficial and generalized lesions. With localized lesions one must be on guard against mistaking a reticulum cell sarcoma for a reticulum cell variety of Hodgkin's disease.

**3 Lymphocytes** Prevalence of medium-sized to large lymphocytes, especially when they are associated with cells resembling the punctate variety of reticuloendothelial cells, has the same prognostic value as the presence of the latter. Contrasted to this is the much better prognosis of the 14 cases in which there was predominance of medium-sized lymphocytes without the association of reticuloendothelial cells. Most of this group were instances of atypical or only somewhat typical lesions. The duration in the 5 cases of generalized lesions averaged 43 0/37 5, 14 2/58 2, 1 patient is still alive. The duration in the 3 cases of superficial lesions averaged 71 0/63 6, 19 3/71 0, 2 patients are alive. The 6 cases of localized lesions had an average duration of 103 0/76 5, 44 0/103 0, 4 patients are alive.

A still longer course was found in the group of 5 of 7 cases in which there was a predominance of small lymphocytes without the association of either reticuloendothelial cells or mitoses. These averaged 69 0/56 7, 27 3/69 0.

**4 Polymorphonuclears** Of 18 cases with a prominent polymorphonuclear component, 3 had an extremely short course, 4 6 months after biopsy. In these 3 cases polymorphonuclear cells were prevalent throughout the lymph nodes and apparently there was the added element of frank infection. In 6 other cases of typical generalized lesions with polymorphonuclear cells the postbiopsy duration averaged 30 5 months. This is a much longer course than the expected 12 4 months, as shown in table 1. A shift to the right in the polymorphonuclear cells was associated in most cases with a slightly more favorable course. No correlation of frequency of polymorphonuclear cells with clinical manifestations of fever could be established.

**5 Plasma Cells, Eosinophils** No correlation of the number of these cells with longevity was evident. Prevalence of plasma cells is found more often in cases of localized involvement, especially in inguinal adenopathy and in glands involved for a short time, i. e., early development.

**6 Fibroblast-like Cells or Derivatives Thereof** Fibroblast-like derivatives may signify a reaction of the body to a weak dose of the noxus and thus be associated with a fairly long course. The finding of such fibroblastic derivatives at biopsy, however, does not necessarily signify a long postbiopsy course. The involvement of lymph nodes and the disease may have existed a long time be-

fore any local or systemic complaints brought the patient to the hospital.

**Preservation of Follicles** No special effect on duration could be attributed to preservation of a few peripheral follicles, except in those cases in which it constituted one of the elements of atypicality.

**Vascularity** Similarly, vascularity of the lymph nodes is another and important element in the atypical picture. Eleven cases of such vascularity were found in this series. Three patients with typical lesions and 1 with atypical lesions with mitosis had a course consistent with their histologic pictures. Of the remaining 7 patients, 6 are alive, with durations averaging 128 3 months postnodal and 74 3 months postbiopsy. The seventh patient died 38 months after biopsy. Five of these 7 patients had localized cervical lesions, 1 localized inguinal and 1 generalized.

*D Correlation of Duration with Clinical Manifestations*—**1 Cutaneous Manifestations** Forty-three patients had complaints referable to the skin. Thirty had pruritus, in 21 of these this was the only cutaneous manifestation. The patients with typical generalized lesions had durations consistent with the histologic picture. Five patients with atypical generalized involvement had an average duration of 82 0/50 4, 31 0/82 0. The symptoms of 2 patients with an atypical histologic picture began with involvement of the skin. The first patient is still alive (60/60, - / 262→). The second, a man of 62 years, died (9/8, - / 29).

There appears to be a disproportionate number of patients with atypical forms of the disease among those with cutaneous manifestations. Twenty-six of the 43 patients had atypical lesions—an incidence of 60 2 per cent, as against 25 8 per cent incidence of atypical lesions in the whole series.

**2 Osseous Involvement** The incidence of infiltration of bone is unavoidably dependent on the thoroughness of roentgen examinations and autopsies. It will therefore vary considerably in reports from various sources. Thirty-three cases with such infiltration were met in this series (14 7 per cent). Thirteen of the patients had typical generalized forms of Hodgkin's disease and had an average postnodal duration of 41 6 months, 3 patients with typical superficial lesions had an average duration of 87 6 months. The duration in these cases is considerably above that in the general series. Apparently osseous involvement occurs and/or is detected in cases lasting longer.

A cursory scanning through the duration of the cases with osseous involvement tempts one

to postulate some protective influence of osseous infiltration. Actually, no basis for such a conclusion can be established. The patients whose biopsies showed prevalence of reticulum cells and/or mitoses had the usual short course. Ten patients with typical generalized lesions had an average duration of 17 months, and that of 3 with typical superficial lesions was 6.6 months, after detection of osseous infiltration.

**3 Fever.** Considered independently, exhibition of fever had no perceptible influence on the course of Hodgkin's disease.

**E Incidence of Hodgkin's Disease.**—Most textbooks of medicine and pathology state that Hodgkin's disease is mostly a disease of early middle age, 20 to 40 years. Uhlenhuth<sup>2</sup> has contradicted this teaching. He has claimed that an analysis of the number of people dying each year from Hodgkin's disease relative to the number of people of that age group in the population shows a steady increase in incidence with age. Thus he has computed that at 10 years there is an in-

TABLE 3—Incidence of Hodgkin's Disease by Decades in the Cases of Typical Generalized Lesions

	20-29	30-39	40-49	50-59	60-69
First 48 cases	1	3	12	1	1
Last 48 cases	1	6	35	3	3

cidence of 62 per 10,000,000, and at 30 years, of 180 and that at 60 years the incidence has increased to 220, with a slight decrease after 60 years. The reason why it is thought to be most prevalent in the 20 to 40 year age group is that absolutely this age group is the most numerous among adults.

This series of 225 cases tends to support Uhlenhuth's contention. The material, which covers eleven years, represents the cases of Hodgkin's disease from a fairly constant fraction of a definitely segregated age group. In 1930 the average age of the World War I veteran was about 36 years. During the first five years of this selective study period (1930 to 1935) the majority of the veterans were in the late thirties. In the last five years the majority of the veterans were in the forties. This is consistent with the finding of an average age of 37.4 years at onset of the disease in the first 39 cases of generalized typical Hodgkin's disease exclusive of those showing prevalence of reticulum cells and mitoses. During the last five years, as the veteran population grew older, the last 39 such cases showed an average age of 43.5 years at onset.

2 Uhlenhuth, P., and Wurm, K. Present Status of Knowledge on Etiology of Hodgkin's Disease, *Deutsche med. Wchnschr.* 66:785, 1940.

This makes a difference of (43.5 minus 37.4) six and one-tenth years, corresponding closely with the elapsed five and a half years in the aging of the veterans. Table 3 lists the incidence by decades. It clearly shows that Hodgkin's disease is not a disease mostly of the 20 to 40 year age period. This fact is further strikingly

TABLE 4—Duration by Decades of Generalized Typical Hodgkin's Disease Exclusive of Hodgkin's Lymphoreticuloma

Decade	Number of Cases	Number of Patients Still Alive	Postnodal Duration
30-39	34	1	42.2
40-49	37	4	23.6
50-59	4	None	20.5

brought home by the occurrence of approximately the same number of cases (20) per year in the eleven year period, even though one started with a fairly constant segment of population of veterans averaging 36 years old and concluded with veterans of 47 year average age.

Gilbert concluded that the most favorable cases are those in which the patients are in the twenties and thirties. When the typical cases of generalized lesions were segregated into decades, a gradually shorter course was found to be associated with increasing age, as detailed in table 4.

The 4 patients with Hodgkin's disease who were in the sixties exhibited a still much shorter postnodal course, namely 12 months. One could readily attribute this short course to the fact that the average life expectancy has its termination at

TABLE 5—Relation Between Age of Onset of Hodgkin's Disease and Prevalence of Reticulum Cells and/or Mitoses

Type of Disease	Average Age at Onset of Hodgkin's Disease			
	Without Prevalence of Reticulum Cells and/or Mitoses		With Prevalence of Reticulum Cells and/or Mitoses	
	Number of Cases	Average Age at Onset, Yr	Number of Cases	Average Age at Onset, Yr
Typical generalized	70	40.4	17	46.4
Atypical generalized	17	39.3	12	46.6
Typical superficial	26	38.7	5	42.0
Atypical superficial	11	40.4	4	42.2

or in this decade. However, closer scrutiny brought out the fact that the lesions of 3 of the 4 patients in the sixties had the histologic feature of prevalence of reticulum cells and/or mitoses. A similar tendency for prevalence of reticulum cells and/or mitoses to occur in the older age group was found throughout the whole series. Details are given in table 5.

*F Weighting of Material*—This series of 225 cases of Hodgkin's disease consisted entirely of male patients, the majority of whom were in the lower income level. Hence the statistical figures should be weighted for sex and economic stratum. Wallhauser<sup>3</sup> mentioned hard work, poor food and intercurrent infection in relation to duration of the disease and quoted Gemmell,<sup>4</sup> in whose opinion estrogon has a protective value. Gilbert,<sup>5</sup> too, has expressed the opinion that the disease is milder in women. There were 12 women among the 16 survivors in his reported 73 cases of Hodgkin's disease. Slaughter and Craver,<sup>6</sup> however, did not find such a great difference in prognosis between males and females. In their series the males had a 16 per cent five year survival rate and the females 21 per cent. A definite opinion as to the comparative mildness of Hodgkin's disease in women is not possible without reference to and statistical analysis of the histologic picture.

## SUMMARY

The clinical histories of 225 cases of Hodgkin's disease were reviewed and the microscopic slides of 186 of these cases, inclusive of 67 autopsies, were restudied.

Before one can be in a position to comment on the role various clinical factors play in the course of the disease one has to know the exact disease entity and histologic picture that one is dealing with.

In the great majority of cases there is sufficient uniformity in the several sections of one lymph node or in several simultaneously taken biopsy specimens from varying sites to warrant the characterization of each case on the basis of the histologic picture.

The outstanding ominous determinant of prevalence of reticulum cells with associated mitoses is statistically of such compelling nature as to warrant—nay, require—a nomenclature based primarily on the histologic features shown by biopsy. Such a nomenclature, listing the types in the order of increasing duration of the course, has been suggested.

The favorable elements in the atypical histologic picture of Hodgkin's disease comprise preservation of follicles, intact capsule, fibrosis, trabeculation or tendency to giant follicle formation,

vascularity, presence of derivatives or fibroblast-like cells and persistence in abundant numbers of the small lymphocytic element of the node.

The extent of involvement bears a direct relation to the course, being second in importance only to the histologic features. Truly localized lesions in the cervical and axillary regions do occur, and these have a much more favorable prognosis.

The inguinal involvement, though clinically localized, appears to have the same significance as generalized spread.

The incidence of Hodgkin's disease is not confined mostly to the 20 to 40 year age group. This fact is strikingly brought home by the occurrence of the same number of cases (approximately 20) per year in the eleven year period, even though one started with a fairly constant segment of

TABLE 6—Average Duration in Months of Two Hundred and Twenty-Five Cases of Hodgkin's Disease

	Total After Onset of Symptoms	After Appearance of Nodes	After Biopsy
Generalized			
Hodgkin's lymphoreticuloma, typical	18.7	16.5	10.6
Hodgkin's lymphoreticuloma, atypical	9.6	8.6	4.2
Hodgkin's granuloma	34.9	32.3	21.8
Hodgkin's lymphoma, atypical	61.7	61.0	49.7
Superficial Multiple Glandular			
Hodgkin's lymphoreticuloma, typical	21.0	21.0	10.0
Hodgkin's lymphoreticuloma, atypical	14.0	12.2	8.0
Hodgkin's granuloma	50.0	48.1	36.8
Hodgkin's lymphoma, atypical	107.7	86.4	67.6
Localized			
Hodgkin's granuloma, inguinal	43.8	43.8	19.6
Hodgkin's granuloma, cervical (the dead patients)	84.6	84.6	17.6
Hodgkin's granuloma, cervical (patients still alive)	133.6→	133.6→	128.0→

population of veterans of 36 years average age and concluded with veterans of 47 years average age.

This study showed increased frequency of the lymphoreticuloma type of Hodgkin's disease, with its sarcomatous features, in the older age group. This contributes to the worse prognosis of the disease in older patients. In fact, the reported incidence of Hodgkin's disease in the older age group will vary as one does or does not include the lymphoreticuloma type, especially in cases in which autopsy is not performed, so that the pathologist is not given the opportunity to see the typical picture of Hodgkin's disease developed.

The average duration in the groups of cases of sufficient number for statistical significance is summarized in table 6. The patients have been segregated according to the histologic picture shown by biopsy and the extent of involvement.

3 Wallhauser, A. Hodgkin's Disease, *Arch Path* 16: 522 (Oct.), 672 (Nov.) 1933.

4 Gemmell, A. A. Menstruation and Pregnancy in Hodgkin's Disease, *J Obst & Gynaec Brit Emp* 30: 373, 1923.

5 Gilbert, R. Le traitement de la granulomatose maligne par la radiothérapie, *J de radiol et d'electrol* 22: 577, 1938.

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## GROUP A HEMOLYTIC STREPTOCOCCUS ANTIBODIES

### III A STUDY OF THE SIMULTANEOUS INFECTION OF A LARGE NUMBER OF MEN BY A SINGLE TYPE \*

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It is well known that varying amounts of circulating antibacterial and antitoxic antibodies are present in the serums of many persons, that increases in these immune substances may be expected to occur following infections and that the magnitude of the immune response differs from individual to individual. Rarely, if ever, have actual measurements of these antibodies been made for large groups of human subjects simultaneously infected with a single strain of micro-organism.

An unusual opportunity to perform such studies became available recently when an outbreak of streptococcal pharyngitis occurred in an Army camp. Many of the clinical details of this epidemic have been described elsewhere,<sup>1</sup> but they may be summarized here. Within sixty hours more than 300 men were admitted to the hospital suffering from typical hemolytic streptococcus tonsillitis or pharyngitis of varying degrees of severity. Approximately 20 per cent of them had a rash and presented the clinical picture of scarlet fever. None of the men died, and only minimal suppurative or nonsuppurative complications were observed. All were treated with the usual amounts of sulfathiazole.

The source of the epidemic could not be traced, but hemolytic streptococci, all of which were mucoid members of group A and of the Griffith subtype 15, were demonstrated in nearly all of the throat cultures obtained from approximately 10 per cent of the group. Infection in similar epidemics usually has occurred through the con-

sumption of milk contaminated by hemolytic streptococci, and it is reasonable to suppose that these men simultaneously ingested streptococci in some article of food.

For the purpose of this study, 118 men, who entered the hospital during one interval of twenty-four hours and who had thus undergone similar incubation periods before the appearance of active infection, were selected for observation. Serums were collected on the fourth day of the disease and again on the twenty-first day. Clinical observations were also made in each case, some of which will be presented in this report.

The antistreptolysin titers of all of the serums were determined, as were agglutinins for the homologous type of streptococci. These observations will now be described in detail.

#### METHOD

Serums were collected in the usual manner and stored at 5 C until used. Antistreptolysin titers were determined by the method of Coburn and Pauli,<sup>2</sup> a single lot of streptolysin being used for all tests. Agglutinins were studied by a slide technic previously described.<sup>3</sup> The methods for the performance of throat cultures and for the serologic identification of the isolated hemolytic streptococci have also been presented elsewhere.<sup>4</sup>

#### RESULTS

*Antistreptolysin Titers*—Initial Levels. The distribution of the studied subjects by initial antistreptolysin titers is presented in table 1 and the chart. It will be observed that the group with titers from 50 to 250 units included nearly

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The work described in this paper was done under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Stanford University.

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2 Coburn, A F, and Pauli, R H. Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process, *J Exper Med* **62** 129, 1935.

3 Rantz, L A, Kirby, W M M, and Jacobs, A L. Group A Hemolytic Streptococcus Antibodies I. Griffith Type Agglutinin and Antistreptolysin Titers in Normal Men and in Acute Infection, *J Clin Investigation* **22** 411, 1943.

4 Rantz, L A. The Hemolytic Streptococci: Studies on the Carrier State in the San Francisco Area with Notes on the Methods of Isolation and Serological Classification of These Organisms, *J Infect Dis* **69** 248, 1941. The Serological Typing of Hemolytic Streptococci of the Lancefield Group A, *J Clin Investigation* **21** 217, 1942.

all of the men and that no definite peak incidence occurred within this range, 39.8 per cent had levels above 125 units.

The relationship between the initial antistreptolysin titers and the nature of the patient and the clinical disease was studied, and two facts emerged. First, there was no definite correlation between the presence of a rash, indicating a lack of immunity to the erythrogenic toxin of the hemolytic streptococcus, and the initial antistreptolysin titer. Subjects with rash were found to be evenly distributed through the entire antibody range. Second, as the antibody levels increased from 50 to 250 units, there was a fairly regular decrease in the percentage of tonsillectomized patients. These data are summarized in table 1.

**Antistreptolysin Response**—The antistreptolysin titers of 118 patients were determined twenty-one days after the onset of the acute illness, and the results were compared with the initial titers, obtained on the fourth day. The results are

TABLE 1—*Distribution of Subjects According to Initial Antistreptolysin Titer*

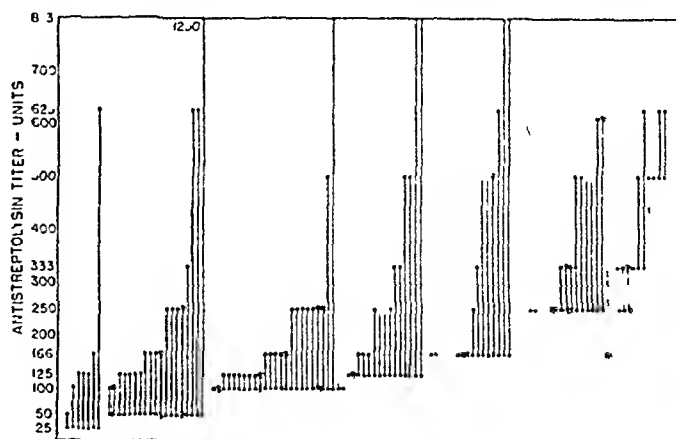
Initial Anti-strepto-lysin Titer	All Subjects	Per Cent of All Subjects	Number with Rash	Per Cent with Rash	Number Tonsillec-tomized	Per Cent Ton-sillec-tomized
25	8	6.8			1	12.5
50	21	17.8	4	19.0	6	28.5
100	25	21.2	6	24.0	6	24.0
125	17	14.4	1	5.9	2	11.7
166	17	14.4	3	17.6	1	5.9
250	18	15.2	6	28.5	1	5.5
333	8	6.8	3	37.5	2	25.0
500	4	3.4				
Total	118		23		19	

portrayed in the chart. The most striking feature of these observations is the great difference in magnitude of antistreptolysin response within the group. Thus, there was a fourfold or greater increase in titer in 11 per cent and no increase in 28 per cent. No correlation was observed between the presence or absence of rash or the severity of the clinical disease and the antistreptolysin response.

Certain relationships between these antibody levels in the acute and in the convalescent stage of the disease are further analyzed in table 2. The subjects have been divided into groups on the basis of the initial antistreptolysin titer, and it will be noted that the average final titer increased from lower to higher levels. Most interesting, however, was the fact that the ratio of average final titer to initial titer decreased. The patients with initial levels below 100 units had an approximately fivefold augmentation of titer, whereas those with levels of 250 or more units exhibited little increase. Similar results were observed when the actual number of men showing an antibody response were considered. An increase in titer occurred in 90.7 per cent of

those with initial levels of 100 units or less and in only 46.8 per cent of those with levels of 166 units or more.

**Study of Type-Specific Agglutinins**—The development of agglutinins for the homologous Griffith type of hemolytic streptococcus was studied.



Antistreptolysin titers of 118 men with hemolytic streptococcus pharyngitis determined at the onset of the illness (lower dot) and during convalescence (upper dot). A simple dot indicates that no rash was present, a circled dot, that the subject had a rash. The lines of dashes indicate a fall in hemolysin titer.

by the slide technic in 118 of the cases. In 17 instances an increase in agglutinins occurred, the initial serums having given a negative reaction in every case. The final titers were approximately 1:3 in 10 cases, 1:12 in 5 and 1:24 in 2. These are believed to be significant changes. The average increase in antistreptolysin titer was somewhat greater in this group than among the patients in whose serum no agglutinins appeared. There was no apparent correlation between the

TABLE 2—*Relationship of Antibody Response to Initial Antistreptolysin Titer*

Initial Anti-strepto-lysin Titer	Total Subjects with Each Antibody Level	Average Final Anti-strepto-lysin Titer, Units	Ratio Average Final Titer Initial Titer	Number with No Response	Per Cent with No Response
25	8	163	6.7	1	12.5
50	21	222	4.4	1	4.8
100	25	211	2.1	3	12.0
125	17	310	2.5	4	23.5
166	17	345	2.1	9	52.9
250	18	360	1.4	9	50.0
333	8	323	0.99	5	71.5
500	4	522	1.05	2	50.0
Total	118			34	

development of these antibodies and the clinical course of the disease, but the number of cases was too small for detailed analysis.

#### COMMENT

The outbreak of hemolytic streptococcus tonsillitis described in this paper offered what may have been a unique opportunity to study certain features of group A hemolytic streptococcus antibody mechanics in human beings under con-

trolled conditions. The simultaneous infection of a large group of men of similar age by streptococci of a single type created an experiment which usually may be secured only in the laboratory in animals. The study of the antistreptolysin content of serums of 118 patients obtained during the acute stage of the illness and three weeks later, during convalescence, was instructive.

It is believed that the antibody titers of the serums obtained on the fourth day are comparable to those present at the onset of the infection. Experimental evidence<sup>5</sup> indicates that a demonstrable increase in the antistreptolysin or agglutinin titer of the serum rarely occurs before the seventh day following the onset of septic sore throat. Relatively few studies of antistreptolysin titers during the first week of such infections have been described, but the reports of Longcope<sup>5</sup> and Lippard and Johnson<sup>6</sup> tend to support this view.

Great differences in the amount of this antibody present initially were demonstrated, which permitted a correlation between these values and various features of the clinical disease. Those pertaining to the course of the illness and complications will be presented elsewhere. It was of interest to learn that there was no relationship between the initial level of antistreptolysin and that of the neutralizing antibody for the erythrogenic toxin, as expressed by lack of development of a rash.

It has been previously demonstrated<sup>7</sup> that the rash toxin is antigenically distinct from the labile toxins, of which the hemolysin is one, and this conclusion was amply confirmed in this study. It seems probable that several of these men, who had high antistreptolysin titers at the onset of their disease but in whom an erythema developed, had previously undergone infection by hemolytic streptococci which ineffectively formed erythrogenic toxin, so that high levels of antistreptolysin developed without the subject's becoming immune to the skin toxin.

Only a small number of the group had undergone tonsillectomy, and it was observed that these men had lower initial antistreptolysin titers

than did the group as a whole. This tends to confirm the indication of the previous study<sup>3</sup> that the presence of hemolytic streptococci in the tonsils of carriers is associated with the maintenance of high levels of antistreptolysin. It was, of course, possible that these men were partially protected against infection by the absence of tonsils and had undergone less frequent and recent attacks of streptococcal disease.

Great differences in the magnitude of antistreptolysin response occurred. This is important, since such variation in the development of antibodies is commonly considered a factor of importance in recovery from various infections but has probably never before been demonstrated under controlled conditions in man.

The ratio of the final antistreptolysin titer to the initial titer varied inversely with the latter, since the patients having the lowest levels during the acute stage exhibited the greatest proportional response. No increase occurred in many men who had high titers at the onset. This indicates that there were definite levels of antibody above which further infection was unable to stimulate increase and that, if response occurred when large amounts of antibody were present, the relative magnitude of the reaction was much less than in the presence of small amounts.

An increased titer of agglutinins for the homologous type of streptococci developed in 14 per cent of the group, the titers being low. This is a less active response than has previously been shown to occur<sup>2</sup> following streptococcal tonsillitis, but it is a further demonstration of individual variation in antibody formation. The increase in antistreptolysin titer appeared to be greater in this group, but there was no correlation between the development of agglutinins and the clinical course of the disease.

#### SUMMARY

A large number of men of comparable age were simultaneously infected by a single type of group A hemolytic streptococci. Antistreptolysin and agglutinin titers in the serums of 118 of these men were measured at the onset of their disease and during convalescence. Great variation in the initial antistreptolysin titers was demonstrated. There was no correlation between the initial antistreptolysin titer and the presence of a rash. There was a relationship between the initial level and the absence of tonsils. Striking differences in the magnitude of antistreptolysin response were observed. These were closely correlated with the initial antibody titer. Fourteen per cent of the group acquired agglutinins for the homologous type of streptococci.

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# THE OSCILLOMETRIC INDEX

AN AID IN EVALUATING THE ARTERIAL STATUS OF THE  
LOWER EXTREMITIES

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MEDICAL CORPS, ARMY OF THE UNITED STATES

AND

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The interpretation of the readings obtained by oscillometry in cases of arterial disease is rendered difficult by the number of factors which may influence the value at any single level of the extremities. For instance, the normal minimum reading at the ankle is given by various observers as  $\frac{1}{2}$ ,<sup>1</sup> 1,<sup>2</sup> 2 to 3<sup>3</sup> and 3.<sup>4</sup> Because of these discrepancies, Atlas<sup>5</sup> compared the oscillometric reading at the ankle with that at the wrist and expressed the result in the form of a ratio. Since arteriosclerotic changes usually progress more rapidly in the lower than in the upper extremity, the reading at the wrist may be assumed to represent each patient's approximately normal value, and Atlas demonstrated that this oscillometric index (ankle/wrist) provides a better basis for evaluation of the arterial status in the leg than does an oscillometric reading at any single level of the extremity. In a series of 90 normal adults, Atlas<sup>5a</sup> found this ratio to be 1 or more, whereas in a series of 100 persons with arteriosclerosis of the lower extremities, the ratio was found to be less than 1. For these patients with low oscillometric indexes, the absolute oscillometric value proved misleading as a criterion of arterial disease of the extremities, since in half of them, despite the absence of pulsation in both the dorsal pedal and the

posterior tibial arteries, the oscillometric reading at the ankle was 1 or more, which is generally accepted as normal. The oscillometric index, however, "enables the examiner to demonstrate in a roughly quantitative way decreased arterial pulsation in the lower part of the leg."<sup>2b</sup>

Our contribution to the problem is the correlation of Atlas' oscillometric index with other objective evidences of vascular disease, namely, results of cutaneous temperature tests and of roentgen examination of the vessels of the lower extremity. Such a correlation should indicate to what extent the oscillometric index of itself aids in evaluation of the arterial status of the lower extremities.

## CLINICAL DATA

Oscillometric determinations were made at various levels, including the wrist, ankle and foot, on 84 ambulatory patients with heart disease. They were unselected with respect to their peripheral vascular status. These patients (63 men and 21 women), in addition to the oscillometric determinations, all had the following special examinations: (1) cutaneous temperature tests of the lower extremity following posterior tibial nerve block, (2) soft tissue roentgenograms of the lower extremities for evidence of calcification of the vessels, and (3) physical examination of the extremities for evidences of arterial insufficiency.

The cause of the heart disease was classified as follows: arteriosclerosis, 40 patients, hypertension, 2, hypertension and arteriosclerosis combined, 29, rheumatism, 6, hyperthyroidism and arteriosclerosis, 1, unknown, 6. The ages ranged from 35 to 80, with an average of 60 years. Results were excluded for patients in whom edema of the legs was present at the time of the oscillometric examination. There were no persons with thromboangitis obliterans in the series.

## TECHNICS

*Oscillometric Index* — After exposing the arms to above the elbows and the legs to the knees, the patient rested in bed for ten minutes before the oscillometric readings were made. The Boulitte or the Collens oscillometer was used, identical readings were obtained with these two instruments. A cuff measuring 2 by 9 inches (5 by 23 cm) was used, for the wrist and ankle readings it was applied so that its lower border reached the styloid and malleolar processes, respectively. The room temperature varied on different days from about 20 to 26 C (68 to 78.8 F).

From the Cardiac Service of Beth Israel Hospital  
1 Montgomery, H., Naide, M., and Freeman, N. E. The Significance of Diagnostic Tests in the Study of Peripheral Vascular Disease. *Am Heart J* **21** 780 (June) 1941.

2 (a) Samuels, S. S. The Diagnosis of Peripheral Arterial Obstruction, *J Lab & Clin Med* **27** 19 (Oct) 1941. (b) Atlas, L. A. Oscillometry in Diagnosis of Arteriosclerosis of the Lower Extremities, *Arch Int Med* **63** 1158 (June) 1939.

3 Bernheim, A. R., and London, I. M. Arteriosclerosis and Thromboangitis Obliterans, *J A M A* **108** 2102 (June 19) 1937.

4 Mufson, I. Intermittent Limping. Intermittent Claudication, Their Differential Diagnosis, *Ann Int Med* **14** 2240 (June) 1941.

5 Atlas, L. A. (a) Oscillometric Readings in Cases of Arteriosclerotic Disease of the Lower Extremity, *Arch Int Med* **66** 155 (July) 1940, (b) footnote 2 b.



In calculating the oscillometric index, the average of the maximum readings obtained at the two wrists was used unless there was evidence of arterial obstruction in one arm due to thrombosis or embolism, in which case the ratio was calculated on the basis of the value obtained on the other arm. The figure obtained in this way was divided into the value for the ankle reading of that extremity on which a cutaneous temperature test had been done. In cases in which cutaneous temperature tests were available for both feet, the oscillometric index for each lower extremity was studied separately (10 cases), but since the oscillometric indexes were essentially the same for the two legs in each case, they were considered as one in the analysis of the data.

In order to test the constancy of the oscillometric index, the index was redetermined on 17 patients within

TABLE 1—Comparison of the Results of Cutaneous Temperature Tests on the Same Extremity at Different Room Temperatures

Patient	Date of Test	Room Temperature, C	Maximum Cutaneous Temperature, C	Change in	
				Room Temperature, C	Maximum Cutaneous Temperature, C
1	9/30/38	23.8	34.3		
	10/20/38	23.7	34.6	-0.1	+0.3
2	9/18/38	25.6	34.0		
	10/18/38	24.6	33.8	-1.0	-0.2
3	11/ 2/38	23.7	33.6		
	12/18/40	21.4	33.0	-2.3	0
4	10/ 3/38	23.8	31.2		
	11/29/38	21.4	31.3	-2.4	-0.1
	2/27/39	20.9	31.8	-2.9	+0.6
5	10/27/38	24.1	33.3		
	12/12/38	20.2	33.3	-3.9	0
6	10/ 3/38	26.6	32.1		
	10/12/38	23.3	31.9	-3.3	-0.2
	12/18/40	22.6	32.2	-4.0	+0.1
7	9/18/38	25.6	31.0		
		20.4	33.5	-5.2	-0.5
8	8/17/38	32.5	33.9		
		23.3	33.1	-9.2	-0.8
9	8/17/38	32.0	32.4		
		21.0	32.7	-11.0	+0.3
10	8/17/38	31.2	33.5		
		17.5	33.3	-13.7	-0.2
Average				-4.9	-0.04

six months after the original observations were made. We found that although the absolute oscillometric readings occasionally changed appreciably, the index usually remained remarkably constant and did not vary by more than 0.2 from the original value. For example, in 1 instance the initial average reading at the wrists was 2.5 and at the ankles 3.0, yielding an index of 1.20; five months later the reading at the wrists was 4.5 and at the ankles 5.5, yielding an index of 1.22.

**Cutaneous Temperature Test**—To measure the radiation from the surface of the skin, the Hardy radiometer was used.<sup>6</sup>

During the course of any given cutaneous temperature test the room temperature was maintained practically constant. For different tests, however, the room

6 Hardy, J. H., and Soderstrom, G. F. An Improved Instrument for Measuring Surface and Body Temperature, *Rev. Scient. Instruments* 8:419, 1937.  
Hardy, J. H. The Radiation of Heat from the Human Body, *J. Clin. Investigation* 13:593 (July) 1934.

temperatures ranged from approximately 20 to 26 C (68 to 78.8 F). It was demonstrated in another series of experiments that such differences in the room temperature did not influence the results (table 1 and chart 1). For one group of patients (patients 1 to 6) the cutaneous temperature test was repeated on the same extremity on different dates. For another group (patients 7 to 10) successive tests were carried out on the same day at different temperatures; an oxygen tent was used to secure the colder environment. It should be noted that results of duplicate tests at different temperatures varying as widely as 13 degrees (C) (23.4 degrees [F]) were not significantly different, for an average change of 4.9 degrees (C) (8.8 degrees [F]) in the environmental temperature, the average change in the vasodilatation temperature was negligible.

The procedure for the cutaneous temperature test was as follows: After exposing the legs to the knees, the patient rested in bed for fifteen minutes before the test was started. The temperature of the skin on the dorsal surface of the great toe of each foot was determined at intervals of five minutes until a constant level was reached or until the temperature of the toe began to decrease. This required from fifteen to forty minutes.

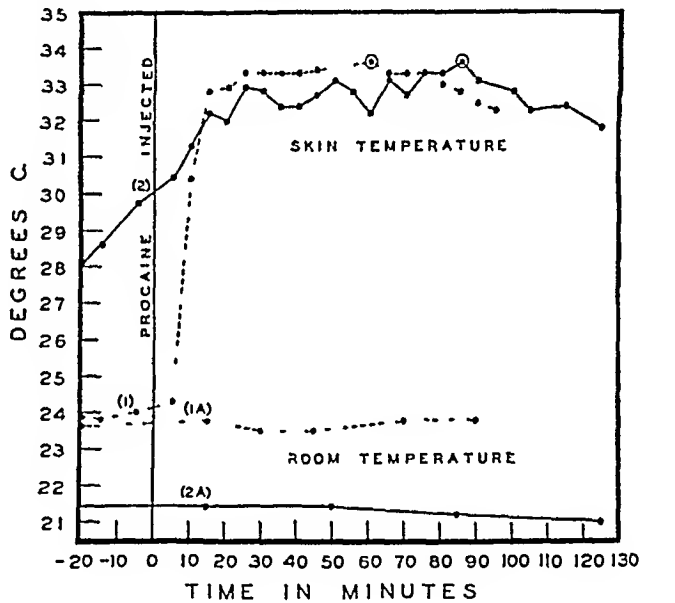


Chart 1 (table 1, patient 3)—Curve 1 shows the cutaneous temperature of the great toe after posterior tibial nerve block determined on Nov. 21, 1938, and curve 1 A, the room temperature during the test. Curve 2 shows the cutaneous temperature similarly determined on the same foot about one month later at a different room temperature, 2 A. Note that the same vasodilatation temperature (33.6 C [92.5 F]) was attained in both tests in spite of a difference of approximately 2 degrees (C) in the room temperature. It is interesting that the oscillometric index in this instance was 0.27, despite the normal vasodilatation temperature.

Block of the posterior tibial nerve was then induced in one extremity by local infiltration with 10 cc of a 2 per cent aqueous solution of procaine hydrochloride. The nerve block was judged satisfactory if there was loss of sensation to light touch on the dorsal surface of the big toe. Results for patients in whom the nerve block was judged incomplete were excluded. During the development of anesthesia, readings of cutaneous temperature were continued at five minute intervals until the readings obtained from the anesthetized toe

had reached and passed a peak, as indicated by declining values. The results of two typical tests are shown in chart 1.

To ascertain the normal vasodilatation temperature under these conditions, we examined 14 patients who were under 35 years of age (average 25 years) and who had mitral valvular disease without clinical evidence of vascular disease of the extremities. In this group the maximum cutaneous temperature after blocking of the posterior tibial nerve ranged from 32.7 C to 34.7 C (90.8 to 94.7 F), with an average of 33.7 C (92.7 F). These results suggest that a value of less than about 32.5 C (90.5 F) may be abnormal. This is in harmony with the figure 32 C (89.6 F) taken by Gibbon and Landis as representing the lower limit of the normal vasodilatation temperature determined under somewhat different conditions.<sup>7</sup>

#### CORRELATION OF THE OSCILLOMETRIC INDEX WITH OTHER TESTS OF ARTERIAL DISEASE

For analysis, the 84 subjects who form the basis of this study were divided arbitrarily into

cutaneous temperature studies increases. This suggests that a value of 0.75 may be regarded as the lower limit of normal, rather than an index of 1.0 as stated by Atlas.<sup>2b</sup>

Calcification, it may be noted (table 2), occurs in 37 to 40 per cent of the patients having a normal oscillometric index. When the index falls below 0.75, the incidence of calcification of the arteries of the lower extremities approximately doubles, when the index falls below 0.51, calcification occurs in 100 per cent of the patients. It is noteworthy that not only the incidence but the extent of calcification increases as the index falls.

The cutaneous temperature test shows a normal average value (33.0 C [91.4 F] or more) until the oscillometric index falls below 0.31, when the vasodilatation temperature declines to an average of 31.8 C (89.2 F) (table 2).

TABLE 2—Correlation of the Oscillometric Index with Other Laboratory and Clinical Data

Oscillometric Index	No. of Cases	Male, per Cent	Average Age (Range), Yr	Dia betes, per Cent	Hyper tension, per Cent	Maximum Cutaneous Temperature After Nerve Block			Calcifi cation,* per Cent	Absence of Pulsa tions,† per Cent	Zero Oscillo metric Reading at Foot, per Cent
						Average (Range), C	32.5 C or Less, per Cent	31.5 C or Less, per Cent			
1.0 or more	33	64	59 (36-76)	15	60	33.2 (31.8-35.9)	13	0	37	0	0
0.99-0.75	20	75	57 (35-73)	5	60	33.4 (31.9-35.6)	15	0	40	0	0
0.74-0.51	11	82	57 (42-80)	9	64	33.0 (32.2-34.0)	27	0	73	0	0
0.50-0.31	7	85	61 (43-70)	43	71	33.2 (31.9-34.7)	23	0	100	43	29
0.30 or less	13	85	62 (50-77)	30	77	31.8 (30.3-33.6)	77	33	100	62	40

\* Vessels of the lower extremities

† Pulsations absent in both dorsal pedal and posterior tibial arteries

several groups according to the oscillometric index: those with an index of 1.0 or more, those with indexes of 0.99 to 0.75, 0.74 to 0.51 and 0.50 to 0.31 and those with an index of 0.30 or less. It may be seen in table 2 that these groups are essentially comparable with respect to age, sex and incidence of hypertension. The incidence of diabetes mellitus, however, is appreciably higher for the groups with an oscillometric index below 0.51.

A correlation of the oscillometric index with the data secured by other means of examination shows (table 2), first, that the groups with an index of 1.0 or more and the one with an index of 0.75 to 1.0 are essentially similar and, secondly, that as the oscillometric index falls below 0.75, the per cent of subjects with abnormal findings by roentgen examination and

Since there is some disagreement in the literature as to what constitutes the lower limit of the normal vasodilatation temperature, the data were analyzed with respect to the per cent of subjects having values below both 32.5 and 31.5 C (90.5 and 88.7 F). With use of either of these figures it may be seen that the most striking rise in the incidence of abnormal cutaneous temperatures occurs when the oscillometric index falls below 0.31. It should be noted, however, that in this lowest range of the oscillometric index, the vasodilatation temperature was normal in 3 instances. A correlation of the oscillometric index with the vasodilatation temperature is shown in chart 2.

In the case of the clinical examination, the incidence of absence of pulsations on palpation of the dorsal pedal and posterior tibial arteries increases sharply when the oscillometric index falls below 0.51. This fact is substantiated by a similar observation with respect to the incidence of a zero oscillometric reading at the foot (table 2). For the group of subjects with an

<sup>7</sup> Gibbon, J. H., Jr., and Landis, E. M. Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J. Clin. Investigation* 11:1019 (Sept.) 1932.

oscillometric index in the lowest range (below 0.31), the clinical diagnosis was arteriosclerosis obliterans. These patients all had physical signs of arterial insufficiency, including pallor on elevation and rubor on dependency, 6 had intermittent claudication, but in all the subjects physical

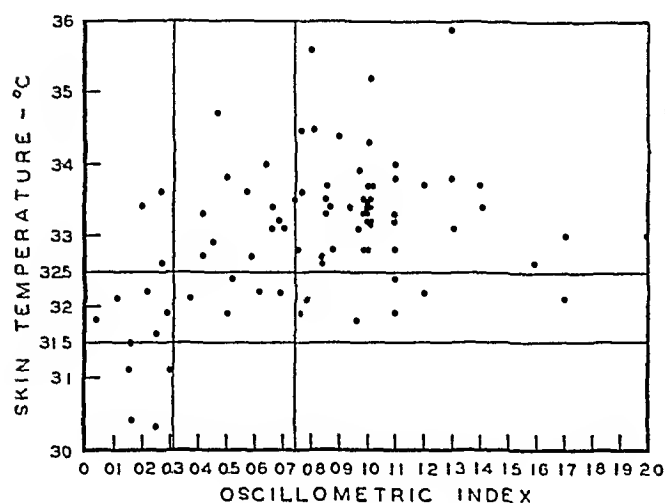


Chart 2—Correlation of the oscillometric index and the cutaneous temperature after posterior tibial nerve block for 84 subjects

activity was limited by a low cardiac reserve. All had extensive calcification on roentgen examination. The cutaneous temperature test confirmed the presence of occlusive arterial disease in 10 of the 13 subjects, in these 10 the vasodilatation temperature ranged from 30.3 to 32.2 C (86.5 to 90 F), with an average reading of 31.4 C (88.5 F), in the other 3 subjects, the vasodilatation temperatures were 33.6 (92.5 F) (duplicate readings on 2 tests as shown in chart 1), 33.4 (92.1 F) and 32.6 (90.7 F), respectively.

The finding of a normal vasodilatation temperature together with a low oscillometric index is perhaps surprising. A possible explanation is that the lowering of the oscillometric index for these persons is the result of an extremely inelastic vessel wall due to heavy calcification of one or more large arteries in the leg, while the relatively nonpulsatile arterial flow through the pipestem vessel remains adequate. Another possibility is that adequate collateral circulation has been established in the foot after occlusion of a section of one of the larger arteries above the ankle, the development of adequate collateral flow under these conditions has been demonstrated by means of arteriography.<sup>8</sup> In view of

the positive clinical signs of arterial insufficiency in these subjects, it appears that occasionally the oscillometric index may be a more reliable guide to the presence of arteriosclerosis in the lower extremity than is the cutaneous temperature test.

The data were analyzed to determine whether a single oscillometric reading at the foot or ankle would yield as much information regarding the arterial status as does the oscillometric index. Chart 3 shows that in general there is a correlation of the ankle reading with the oscillometric index. Thus, no patient with an ankle reading above 4.0 had an oscillometric index below 0.75, and no patient with an ankle reading of less than 1 had an oscillometric index above 0.3 or a vasodilatation temperature above 32.5 C (90.5 F). However, it may be seen that for ankle readings between 1 and 4 the oscillometric index and the vasodilatation temperature vary widely, yielding both normal and abnormal values, hence an ankle reading which falls in this range must be regarded as ambiguous. A comparison of the oscillometric reading at the foot with the oscillometric index (table 3) similarly shows that oscillometric readings at the foot which fall in the range of  $\frac{1}{8}$  to 2 are ambiguous, since the oscillometric index for these patients varied from 0.3 or less to 0.75 or more. However, no patient with a reading at

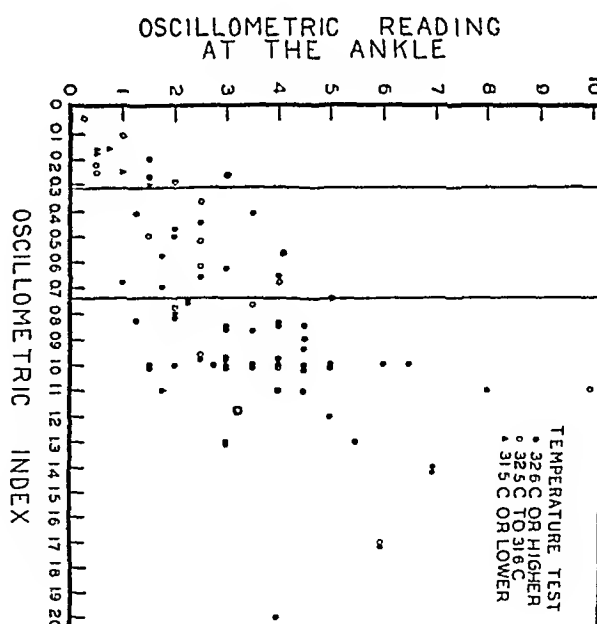


Chart 3—Correlation of the oscillometric index, the oscillometric reading at the ankle and the cutaneous temperature after posterior tibial nerve block for 84 patients

<sup>8</sup> Yates, W. W. Maintenance of the Functional Integrity of Occluded Large Arteries as Demonstrated by Thorotrast Arteriography, *Am J M Sc* 194 372 (Sept) 1937

the foot of more than 2 had an index less than 0.75, and no patient with a zero oscillometric reading at the foot had an oscillometric index above 0.3. It is apparent that the oscillometric

index is, in general, more useful in evaluating arteriosclerosis of the lower extremity than is the oscillometric reading at the foot or ankle when the latter readings fall within these intermediate ranges

#### SIGNIFICANCE OF OBJECTIVE TESTS IN CASES OF ARTERIOSCLEROSIS OF THE LOWER EXTREMITY

The data were next analyzed to answer, if possible, certain questions relating to the life history of arteriosclerosis in the lower extremity and to criteria for the diagnosis of this condition. First, which of these objective tests—the soft tissue roentgenogram, the oscillometric index and the cutaneous temperature test—yields the earliest clue to the existence of arteriosclerosis in this part of the body, second, how often does each test provide the sole evidence of arteriosclerosis, and, third, can any one test alone be relied on to establish this diagnosis?

TABLE 3—*Comparison of the Oscillometric Reading at the Foot with the Oscillometric Index*

Oscillometric Index	Total No of Cases	Oscillometric Reading at the Foot				
		0 Per cent	1/4 to 1/2 Per cent	5/8 to 1 Per cent	1 1/4 to 2 Per cent	2 1/2 or More Per cent
0.75 or more	53	0	34	30	29	7
0.74 to 0.51	18	11	40	39	10	0
0.50 or less	13	30	46	24	0	0

It is apparent that roentgen examination usually affords the earliest evidence of this condition, for calcification of the vessels was noted in about 38 per cent of the group with a normal oscillometric index. None of these 20 patients with calcification had clinical evidence of arterial insufficiency, and the vasodilatation temperatures were also normal, except possibly in 2 instances (32.2 and 32.1 C [90 and 89.8 F], respectively). Excluding these 2, calcification was the sole abnormality demonstrable by these three tests in 21.4 per cent of the series of 84 subjects.

A low oscillometric index was the sole abnormality in 2 of the 11 subjects for whom the index fell in the intermediate range of 0.74 to 0.51, or in approximately 2.4 per cent of the series of 84 subjects. In 1 additional instance an oscillometric index of 0.62 was associated with a vasodilatation temperature of 32.2 C (90 F). When the oscillometric index was 0.5 or less, calcification was always present and frequently a low vasodilatation temperature and clinical signs of arterial insufficiency were noted.

When the vasodilatation temperature was in the lowest range, below 31.5 C (88.7 F), all

other methods of examination which were employed revealed arterial disease of the lower extremities. However, the cutaneous temperature test was the only objective technic suggestive of such pathologic change in 3 of the 12 subjects with vasodilatation temperatures below 32 C (89.6 F) and in 5 of the 22 subjects with vasodilatation temperatures below 32.5 C (90.5 F). These figures represent 3.5 and 6.0 per cent respectively of the series of 84 subjects.

Thus at the two extremes were the group (18 subjects) with minimal functional changes, in whom the vascular examination revealed nothing abnormal except calcification, and the group (20 subjects) with advanced arterial insufficiency, in whom several or all of the tests yielded abnormal results. In an intermediate group (46 subjects) we should have been uncertain as to the existence of arterial disease except for the oscillometric index in 2 instances (4.3 per cent) and the vasodilatation temperature (below 32.5 C) in 4 (10.9 per cent). The soft tissue roentgenogram seems to be the most reliable, though not an infallible, technic for the detection of the mere presence of arteriosclerosis but no single test can be relied on to establish this diagnosis in all cases. Judgment as to the course of arteriosclerosis or the degree of occlusive disease ideally should be based on examinations which include determination of both the oscillometric index and the vasodilatation temperature.

#### PRACTICAL VALUE OF THE OSCILLOMETRIC INDEX

In evaluating the usefulness of the oscillometric index, one should consider the test in relation to several diagnostic problems. The first of these is how to distinguish intermittent pain in the lower extremity which is of non-vascular origin from that which is due to arterial insufficiency. As Mufson<sup>4</sup> has pointed out the differentiation of intermittent limping due to orthopedic or neurologic changes from intermittent claudication due to peripheral vascular disease presents many difficulties, he noted however, that "an equally normal oscillometric reading on both legs is the most dependable sign of a competent peripheral vascular system." Since our data show that the oscillometric index is a more reliable guide to arterial function than is the absolute oscillometric reading at either the foot or the ankle, it would follow from this statement that the oscillometric index is the most useful single technic to determine whether the pain is or is not due to arterial insufficiency.

In the presence of a normal oscillometric index, one may be assured that this symptom is not due to arteriosclerosis.

The second problem is as follows. Given a patient with arteriosclerosis and arterial insufficiency of the lower extremities, how may one discover what role the factor of spasm and what role the factor of organic narrowing of the lumen plays in the occlusive process? The cutaneous temperature test after nerve block yields the final answer to this question. Our data show, however, a close, although not perfect, correlation between the results of the cutaneous temperature test and the level of the oscillometric index. Thus, a small proportion (13 per cent) of the subjects with a normal index (0.75 or more) had vasodilatation temperatures within the borderline range of 32.5 to 31.5 C (90.5 to 88.7 F) and none had a cutaneous temperature below 31.5 C (88.7 F), whereas nearly half of the patients with a very low index (0.3 or less) had a vasodilatation temperature in this borderline range and in one third the cutaneous temperature was below 31.5 C (88.7 F). Such a correlation is to be expected, because the lower extremities are usually affected by arteriosclerosis earlier and to a greater degree than are the upper extremities, this fact has been particularly well demonstrated by Sappington and Horneff by means of microscopic comparisons of the tibial and radial arteries for the different decades of life.<sup>9</sup> Because of the general parallelism between the oscillometric index and the cutaneous temperature after nerve block, a fairly reliable judgment can be made by means of the former, simpler, technic as to the relative roles played by organic occlusive disease and by functional spasm in the production of arterial insufficiency.

A third problem relates to the evaluation of the arterial status in a patient who is found by roentgenogram to have calcification of the vessels of the lower extremities. The incidence of this abnormality in the absence of symptoms is perhaps surprisingly high. Thus Sappington and Horneff<sup>9</sup> reported that sections of the tibial artery showed calcification in 37 per cent of a group of patients 41 to 60 years of age presenting no definite signs of arterial obstruction in the extremities. This figure is in close agreement with the 38 per cent incidence of calcification observed by roentgenogram in our series of 53

patients of similar age and with an oscillometric index above 0.75, these patients also showed no evidence of arterial insufficiency. How this situation arises has been explained by Hines and Barker.<sup>10</sup> "In arteriosclerosis obliterans, calcification and other forms of degeneration of the medial coat have no clinical significance in themselves, inasmuch as they do not cause significant interference with the flow of blood. The important component of the lesion present in arteriosclerosis obliterans seems to be the atheromatous plaque, because this is responsible in itself for partial occlusion of the lumen, and it is the locus for the development of the thrombus which completes the occlusion." Since in our series lowering of the oscillometric index below 0.75 is associated with a progressive increase in the incidence of calcification up to 100 per cent for the lowest indexes and with an increase in the incidence of abnormal cutaneous temperatures, an abnormal oscillometric index may be taken to indicate that the atheromatous occlusive process is being superimposed on the medial calcification. Thus it appears that the level of the oscillometric index provides a satisfactory guide to the degree of the occlusive process even in the presence of calcification of the vessels.

#### SUMMARY AND CONCLUSIONS

The oscillometric index (ratio of the oscillometric reading at the ankle to that at the wrist), the cutaneous temperature following posterior tibial nerve block and the presence or absence of calcification of the vessels of the lower extremities in the roentgenogram were determined for 84 ambulatory patients with heart disease.

A correlation of the data obtained by these three laboratory aids (oscillometry, cutaneous temperature test and soft tissue roentgenogram) shows that as the oscillometric index decreases the incidence and extent of calcification of the vessels of the lower extremity and the incidence of abnormal cutaneous temperatures increase.

In the presence of a normal circulation in the upper extremity, an oscillometric index of 0.75 or more almost always indicates adequate arterial function in the lower extremity. Similarly an index of less than 0.75 indicates sclerotic changes in the arteries of the leg, probably with calcification, and an index of 0.3 or less indicates extensive calcification and probably advanced occlusive arterial disease.

<sup>9</sup> Sappington, S. W., and Horneff, J. A. Tibial Artery Changes in Comparison with Those of the Radial and Coronary Arteries, *Am J M Sc* **201**: 862 (June) 1941.

<sup>10</sup> Hines, E. A., Jr., and Barker, N. W. Arteriosclerosis Obliterans. A Clinical and Pathological Study, *Am J M Sc* **200**: 717 (Dec) 1940.

The oscillometric index is of greater value in estimating the presence and degree of arteriosclerotic disease in the lower extremity than is the oscillometric reading at the foot or ankle when the latter readings fall within an intermediate range of about 1 to 4 at the ankle and  $\frac{1}{8}$  to 2 at the foot

An oscillometric reading of more than 4 at the ankle or more than 2 at the foot nearly always indicates normal arterial flow, and a reading of less than 1 at the ankle or 0 at the foot indicates occlusive arterial disease

Roentgen examination for calcification of the vessels usually affords the earliest evidence of arteriosclerosis of the lower extremities

Final appraisal as to the degree of occlusive arterial disease of the lower extremities ideally should be based on examinations which include determination of both the oscillometric index and the vasodilatation temperature

Duplicate determinations of cutaneous temperature on 10 patients showed that a variation of several degrees (C) in the room temperature does not materially influence the vasodilatation temperature after posterior tibial nerve block

# Progress in Internal Medicine

## ALLERGY

A REVIEW OF THE LITERATURE OF 1943

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### ALLERGY IN THE ARMY

The Army is cautious about accepting selectees who give evidence of having hay fever, asthma or eczema, and this is proper. The symptoms carry a potential risk of later disability which is often considerable, and so far the methods of dealing with these allergic states are not developed as well as they might be in the Army.

In the First Army Corps Area, Hyde and Kingsley<sup>1</sup> made a study of the incidence of allergy among the registrants at the induction center. There were 60,000 registrants, and of these 21,500 were rejected. Allergy, however, was the cause of less than 1 per cent of the rejections. There were only 495 rejections on account of allergy, and most of these were for asthma. It is interesting that there were only 11 men with eczema and 12 with dermatitis in this large group. Incidentally, the officers reviewed the social classification of the rejected men and found that almost twice as many allergic persons came from the semirural districts as came from the crowded tenement areas. It looks as though allergy were a disease of the country more than of the city.

After selection has been accomplished and training begun, the incidence of allergy appears to increase, and it is higher in this way than it was in World War I. In 1918, only 5 men per hundred thousand were discharged from the Army because of asthma, but from June 1, 1941 to Oct 1, 1942 Blank<sup>2</sup> saw 1,833 patients in the allergy clinic in Fort Eustis, and 78 of these, or 4 per cent, were given disability discharges, all but 3 because of asthma. More recently, Colonel French and Major Halpin<sup>3</sup> have shown what can be done by increasing the knowledge and interest in allergy in one service command. With an expenditure of less than \$500 they were able

to supply testing and treatment materials to 59 different clinics in the Fourth Corps Area. In each station hospital an allergy clinic was organized and the personnel were given special instruction. The result is interesting. Since March 1942, 3,419 Army and 498 civilian patients have been treated. Of these, 1,153 were admitted to the hospital, to stay an average of eighteen and one-tenth days. Of the 3,419 Army patients, 195, or 6 per cent, were discharged from the service, about the same proportion as in Blank's series. On the other hand, 267 men were reclassified and retained in the service. In this series hay fever without asthma accounted for 1,269 cases, while asthma was present in about 1,000. Meantime there were 350 cases of urticaria, 79 of migraine and 138 of eczema. All these figures look large until one considers what might be the total number of men in the Fourth Corps Area. In the *Massachusetts General Hospital News* is an interesting letter which states that in a base hospital in North Africa asthma stood third in the list of medical disabilities (psychic disorders were first, gastrointestinal disease was second, and asthma was third).

It is evident that the problem of allergy is of practical importance in the Army in spite of the effort to eliminate persons who present "significant" symptoms of it. It is to be hoped that the authorities will recognize the accomplishments of Colonel French and will consider better methods, first of recognition and elimination and then of treatment, in case the elimination of this troublesome group of disabilities has not been successful.

### HAY FEVER

Hay fever is still an open problem. There are a few advances this year but not enough. Loveless has continued her studies on the blocking antibody. Last year she<sup>4</sup> made an interesting study on 3 normal volunteer subjects treat-

1 Hyde, R W, and Kingsley, L V. Distribution of Allergic States in Selectees, *J Allergy* **14** 386, 1943.

2 Blank, P. Military Aspects of Allergy, *J Lab & Clin Med* **28** 609, 1943.

3 French, S W, and Halpin, L J. Army Allergy Report on Allergy Clinics in the Fourth Service Command, *Ann Allergy* **1** 1, 1943.

4 Loveless, M H. Immunological Studies of Pollinosis. III. Fluctuations in Antibody-Titer of Normal Individuals Subcutaneously and Intravenously Injected with Pollen Extract Over Protracted Periods, *J Immunol* **44** 1, 1942.



ing them with large doses of pollen extract given at intervals for several months. The blocking antibody was produced in higher concentration by treatment with alum-precipitated (particulate) ragweed than by injections of clear solutions. Also she found that when an extra dose was given after a rest period of several months the concentration of the blocking antibody increased rapidly and to a high level. This result suggests that the perennial method of treating hay fever with doses given at intervals of several weeks throughout the year ought to be more effective than the more conventional preseasonal method. This year in a study reported in a paper read before the American Society for the Study of Asthma and Allied Conditions, Dr Loveless<sup>5</sup> has shown that the titer of the blocking antibody varies in accordance with the symptoms of the patient. She believes that the relief from symptoms depends on the development of this particular antibody.

Hampton and co-workers<sup>6</sup> in Dr H. L. Alexander's clinic at Washington University in St. Louis, have developed a method of detecting the thermostable antibody by a precipitin reaction. Rabbits are inoculated with a suspension of ragweed proteins precipitated by aluminum hydroxide cream, and the resulting immune serum is used to test the excess of ragweed which may remain when the patient's serum is mixed with small quantities of ragweed. If the union between serum and ragweed is firm, no excess results, and there is nothing which blocks the reaction, but if, on the other hand, an excess of ragweed can be demonstrated one can say that not all the ragweed has been combined. The method deserves further study. Frank and Gelfand<sup>7</sup> looked for blocking substances effective for ragweed in other kinds of serum. They found, however, that convalescent scarlet fever serum was unable to inhibit the union of ragweed antibodies with the antigen and that the serum from patients with pneumonia or measles was likewise ineffective.

These researches are important, but one should bear in mind that in hay fever it is the sessile

cellular antibodies which are of particular importance. Dr R. A. Cooke once asked me whether the Widal reaction (a test for antibodies) was a true index of immunity from typhoid fever.<sup>1</sup>

There are other studies of antibodies which do not refer directly to ragweed but which are nevertheless of interest. Kulka<sup>8</sup> found that antigen-antibody mixtures (antipneumococcus serum with specific polysaccharide) fail to stimulate a strip of isolated muscle unless an excess of free antibody is present. Hansen-Pruss and Raymond<sup>9</sup> found that the serum of allergic women contains the highest rate of reagin titer on the last day of menstruation. This titer is in inverse proportion to the level of estrogen. On the other hand, Von Haam and Rosenfeld<sup>10</sup> observed that estrone produced a remarkable increase in specific antibodies when it was given to both castrated and noncastrated rabbits of both sexes previously treated with pneumococcus vaccine.

The question of the specificity of the ragweed antigen is of great practical importance. Simon<sup>11</sup> studied the allergic relationship between the pollens of dwarf and giant ragweed and several of their botanic relatives. First he found that of 40 patients sensitive to the ragweeds 38 reacted to skin tests with other compositae. Serum from 6 of these was mixed with extracts of various pollens, and then the mixture was injected into the skin of nonsensitive recipients. Later the prepared sites were tested with other extracts. The question was whether the allergy resulted from exposure to each species separately or whether the multiple sensitiveness shown by skin tests could be explained on a basis of "crossed reactions." In 4 of the 6 cases dwarf ragweed could have been the only sensitizing agent, for none of the other pollens could neutralize the antibodies for this ragweed. In none of the 6 could cosmos, sunflower, goldenrod or dandelion have been the only sensitizing allergen. Simon's experiments show that the pollens of ragweed and their botanic relatives contain multiple common allergic determinants as well as species-specific allergens. Different persons exposed to this

5 Loveless, M. H. Immunological Studies of Polymiosis. IV. The Accelerated Immune Response in Hay Fever Patients, read before the American Society for the Study of Asthma, New York, Dec. 5, 1942.

6 Hampton, S., Johnson, M. C., Alexander, H. L., and Wilson, K. S. Detection of the "Thermostable" Antibody by Means of the Precipitin Reaction. *J. Allergy* **14**: 227, 1943.

7 Frank, D. E., and Gelfand, H. H. Studies on the Blocking Antibody in Serum of Ragweed-Treated Patients. I. A Search for Inhibiting Substances in Other Types of Immune Serum. *J. Allergy* **14**: 273, 1943.

8 Kulka, A. M. Studies on Antibody-Antigen Mixtures. II. The Effect on Normal Living Excised Tissue and Its Dependence on the Presence of Free Antibody in the Mixture. *J. Immunol.* **46**: 235, 1943.

9 Hansen-Pruss, O. C., and Raymond, R. Influence of the Menstrual Cycle on the Titer of Circulating Allergens. *J. Clin. Endocrinol.* **3**: 81, 1943.

10 Von Haam, E., and Rosenfeld, I. The effect of Estrone on Antibody-Production. *J. Immunol.* **43**: 109, 1942.

11 Simon, F. A. Allergic Relationship of the Pollens of Dwarf and Giant Ragweed to Several of Their Botanic Relatives. *J. Exper. Med.* **77**: 185, 1943.

group of pollens may become sensitized to one or more members in one case and to other members in other cases. Specificity is present, but crossed relationships are frequent and important.

*Pollen Chemistry*—This is important, because the chemical mixtures which constitute routine extracts cause effects which are always hard to interpret. Abramson, Engel and Moore<sup>12</sup> have continued their electrophoretic analyses of pollen. In timothy pollen there is a major component which moves slowly in the electrical field and is colorless, but in addition there are at least six other components which are negatively charged and are pigmented. It is important to note that each one of these fractions elicits a positive reaction in skin tests on sensitive patients.

Cohen and Friedman<sup>13</sup> tried to extend Stull's experiment in which "fraction I" was split off from the crude ragweed extract by half saturating the solution with ammonium sulfate. By a combination of ammonium sulfate precipitation, dialysis, and freezing and thawing, they obtained a purified globulin which appeared to react specifically with its own reagin. They were able to produce crystals which were highly active in direct skin tests and which had a high neutralizing capacity as tested on rabbit anti-ragweed serum. It looks as though Cohen and Friedman had arrived at a fairly pure product.

Harsh and Huber<sup>14</sup> digested the extract of giant ragweed pollen with freshly assayed pancreatin and also with highly active pepsin. The skin test activity of the digest was greatly reduced, but, on the other hand, it was not eliminated entirely.

Finally, Newell,<sup>15</sup> working in the laboratory of physical chemistry at the Harvard Medical School, through the courtesy of Professor Cohn, used ample quantities of materials with good technique and was able to separate what appeared to be a number of separate fractions from the crude ragweed material. Some of these were obtained by concentrated phosphate buffers, others by precipitation with ethyl alcohol and still others by precipitation with ammonium sulfate. Each of these fractions was then studied in the Tiselius

apparatus so that the electrophoretic pattern could be determined. Whereas single peaks in the record of the movement of various protein components might indicate a substance of single chemical purity, multiple peaks demonstrate that several different substances are present. Newell found that without exception each of the fractions which he had prepared so carefully was "contaminated", none of them showed a single peak, each of them gave evidence of the presence of some other substance besides the fraction desired. Whereas this work of Newell is not exactly constructive, at least it demonstrates that up to the present time there is no method known by which a pure chemical fraction from ragweed can be obtained.

*Pollen Surveys*—Pollen surveys are interesting. Vaz-Ferreira and Recarte<sup>16</sup> review the allergenic flora of Uruguay. The methods for describing the content of pollen in the air are reviewed by Dahl and Ellis,<sup>17</sup> who recommend that reports include the actual findings, namely, the amount of pollen per unit of area on the slide exposed. The idea has the advantage of simplicity, but still the data will have to be expressed in such a way as to make it easy to compare them with those of other workers.

*Molds*—That the spores of molds are responsible for the symptoms in many obscure cases of hay fever, especially when the reactions to skin tests remain negative, is becoming more and more evident. More studies of molds and of the reactions which they produce are needed. Browning<sup>18</sup> has made a practical study of skin tests with molds on a series of allergic patients as well as on normal persons. Thirty-eight different mold extracts were used—different strains from the genera *Alternaria*, *Aspergillus*, *Hormodendron* and *Penicillium*. From 800 to 1,400 subjects were tested with representatives of each genus, and positive results were obtained in about 25 per cent of the group as a whole. About one third of the mold extracts were too irritating to be of diagnostic importance, the other two thirds gave satisfactory readings, but only a few seemed to have real diagnostic importance.

In the discussion of Browning's paper, Fenberg stated that of 253 patients who had a his-

12 Abramson, A., Engel, M. G., and Moore, D. H. Skin Reactions to Electrophoretic Fractions of Timothy and Pollen Extract, *J. Allergy* **14** 65, 1942.

13 Cohen, M. B., and Friedman, H. J. Preliminary Report on the Fractionation of Ragweed Pollen and Immunologic Studies with These Fractions, *J. Allergy* **14** 368, 1943.

14 Harsh, G. F., and Huber, H. L. Studies of Tryptic and Peptic Digestion of Extracts of Giant and Ragweed Pollen, *J. Allergy* **14** 121, 1943.

15 Newell, J. M. Electrophoretic Studies on the Chemical Fractionation of Ragweed Pollen Extracts, *J. Allergy* **14** 444, 1943.

16 Vaz-Ferreira, R., and Recarte, P. Allergenic Flora of Uruguay, *Arch. Soc. de Biol. de Montevideo* **10** 274, 1942.

17 Dahl, A. O., and Ellis, R. V. The Pollen Concentration of the Atmosphere, *Pub. Health Rep.* **57** 369, 1942.

18 Browning, W. H. Mold Fungi in the Etiology of Respiratory Allergic Diseases, *J. Allergy* **14** 231, 1943.

toiy suggesting alleigy to molds 241 gave positive reactions to skin tests with molds, whereas of 351 patients whose history did not suggest sensitivity to molds only 10 had positive readings

Kurung<sup>19</sup> isolated and identified the fungi in sputum His paper contains a number of beautiful pictures to show the technic and the results

#### ASTHMA

*Physiology and Pathology*—In my review of the literature on alleigy for the year 1941<sup>20</sup> I presented a table which showed that the symptom asthma could be caused by various lesions Spasm and edema of the bronchial mucous membrane constituted one cause, exudate in the tubes, another, obstruction by a foreign body or by a tumor, a third, emphysema, a fourth, and passive congestion in heart disease, a fifth

At a meeting of the Association for the Study of Allergy in June 1942, Lamson read a paper by Lamson, Butt and Stickler<sup>21</sup> reviewing the pathologic observations in 86 cases in which asthma was given as either the primary or the secondary cause of death The patients included 25 women, 57 men and 4 children Of the 86 patients, 24 died primarily of heart disease and had asthma as a secondary diagnosis Three of them had syphilis, 4 had pneumoconiosis and 3 died of morphinism Cancer and tuberculosis were included among other miscellaneous diagnoses This paper shows well that asthma must be regarded as a symptom and not as a disease On the other hand, there is good evidence that death can be produced by asthma without other cause, and in such circumstances the pathologic picture is typical The group studied by Lamson and his associates includes 11 patients in whom the autopsy revealed the presence of tough sticky plugs which occluded the larger and medium-sized bronchi to make a characteristic picture of death by suffocation from asthma itself One should note, however, that 24 is only about 28 per cent of the total group

In children, Cohen<sup>22</sup> has found again that a clinical picture which simulates that of bronchial pneumonia may depend on the formation of tenacious plugs which become more tenacious when

excessive vomiting leads to dehydration and which may occlude a bronchus to produce atelectasis and a low grade pneumonitis in the distal portions Occasionally bronchoscopy is indicated but so far it is his experience that the prognosis is good and recovery occurs

Ayerza's disease is described by Fernandes Pontes and co-workers<sup>23</sup> from the University of São Paulo, in Brazil, as due to a chronic obstructive bronchial pulmonary emphysema The cyanosis indicates a lack of oxygen in the blood and this anoxia stimulates the bone marrow to increase its activity with resulting polycythemia The authors describe 2 cases in which bronchitis had lasted for forty and twenty-two years respectively but the severe dyspnea and cyanosis had been present for only a few months This is interesting because we have been led to believe that Ayerza's disease is dependent in most cases on lesions of the pulmonary vascular system rather than of the lungs and bronchi

More observations are needed on the condition of the cilia in the epithelium of the trachea and larger air tubes Hilding<sup>24</sup> recalls that in the influenza pandemic of 1918 the autopsies on many patients showed the cilia to be destroyed Now he describes a group of patients who died from asthma and other respiratory diseases in whom rather typical changes in the epithelium of the larger air passages were observed In 12 patients large goblet cells were substituted for the normal columnar ciliated cells In 11 the cilia were lost and the bronchi were filled with purulent secretion somewhat as described in Lamson's series These patients also died of suffocation Five patients had bronchial constriction without change in the epithelium One patient died in extreme distress from a severe tracheo-bronchitis, in his case the ciliated epithelium had all disappeared and in addition all the bronchi were filled with viscid plugs As Hilding suggests, it is easy to conceive of a profound disturbance in the normal mechanism by which pulmonary secretions and exudate are removed by the cilia and so to consider how dry sticky plugs can be formed

Cralley<sup>25</sup> studied the ciliary action of the tracheal tree in rabbits He placed his animals

19 Kurung, J M The Isolation and Identification of Pathogenic Fungi from Sputum, *Am Rev Tuberc* **46** 367, 1942

20 Rackemann, F M Allergy A Review of the Literature of 1941, *Arch Int Med* **69** 128 (Jan) 1942

21 Lamson, R W, Butt, E M, and Stickler, M Pulmonary Pathology with Special Emphasis on Bronchial Asthma, *J Allergy* **14** 396, 1943

22 Cohen, S Allergic Respiratory Disease and Pneumonia in Childhood, New Orleans M & S J **94** 440, 1942

23 Fernandes Pontes, J, Jamra, M, and Carvalho da Silva, A Cyanotic Chronic Bronchiopneumopathy Clinical and Physiopathologic Study, *An Fac de med da Univ de São Paulo* **16** 365, 1940

24 Hilding, A C The Relation of Ciliary Insufficiency to Death from Asthma and Other Respiratory Diseases, *Ann Otol, Rhin & Laryng* **52** 5, 1943

25 Cralley, L J Factors Affecting Retention and Rate of Removal of Bacteria from the Tracheal Tree and Lungs, *Am J Hyg* **36** 303, 1942

in a closed chamber and sprayed them with bacteria, and then he made changes in temperature and humidity to see if he could influence the rate at which the foreign substance was removed from the lungs. He found that the normal ciliary function was very effective and it was only when the temperature and humidity were modified to extreme degrees that it was disturbed.

When asthma depends on the retention of sticky material in the bronchi, one understands why bronchoscopy should be advocated. Friedberg<sup>26</sup> reviews the literature and describes the cases of 8 patients who were relieved by bronchoscopy. Four of them, however, were small children in whom the removal of a foreign body removed the asthma also. Patient 5 was a woman who had a broncholith which acted as a foreign body. Patient 6 had a pulmonary abscess, and patients 7 and 8 had stenosis of a bronchus, in 1 of them due to tuberculosis. It is a little disconcerting not to find any of the cases with the pathologic changes which we have called typical Bases and Kurtin<sup>27</sup> maintain that bronchoscopy may be life saving in cases of asthma.

The blood pressure in asthma fluctuates during the phases of respiration. This has been described, but Osgood has investigated the matter in a special study. In 1942<sup>28</sup> he obstructed the tracheas of cats and the mouths of human volunteers. He found that as the respiratory effort increased, the systolic blood pressure fell during inspiration. This year<sup>29</sup> he has studied patients with asthma and found that fluctuations of the systolic blood pressure are a constant finding. The high point occurs during expiration and the low point during inspiration, and the amplitude of the difference is closely parallel to the severity of the asthma. I can add to this that the fluctuation does not occur in all cases and is distinctly greater in older persons who have emphysema than it is in younger patients. I believe that the sign may be of diagnostic importance, but unfortunately the study has not gone far enough to indicate the cause of the drop except to show that it depends on the sucking effect, the increased negative pressure of active inspiration. Whether this affects the output of the right or

of the left ventricle more or affects both at the same time and equally is hard to say.

Somewhat related are the observations of Vaccarezza and Cucchiari Acevedo,<sup>30</sup> from Buenos Aires. In 3 cases of pulmonary tuberculosis associated with asthma they made direct measurements of the intrapleural pressure before, during and after acute paroxysms of asthma. They found that during the attack of asthma there was a definite increase of intrapleural pressure, and in 2 cases in which pneumothorax had been induced they removed some of the air and brought relief from the symptoms. After the attack had been relieved by epinephrine, the collapse of the lungs was even greater than before.

*The Heart*—The heart in asthma is always interesting, partly because the nature of so-called "cardiac asthma" is so obscure and partly because in every case of severe asthma the doctor fears that the heart may give away.

Schiller, Colmes and Davis<sup>31</sup> made special studies of the heart in 69 cases. In 15 of these the patients died and autopsy was performed. In 3 the asthma had lasted for less than three years, and the heart was normal. In 12 the asthma had lasted for over six years, and in 4 of these there were right-sided heart strain and death in failure (cor pulmonale). Of 54 living patients, however, only 1 had any clinical evidence of heart failure. The electrocardiograms, on the other hand, revealed a number of abnormalities. There was deviation of the axis to the right in 18 per cent of the patients whose asthma had lasted for more than ten years. The authors state that cor pulmonale is more common than is usually believed. If a careful study reveals trouble in less than a quarter of the cases it would seem that on the whole the heart keeps going on well in spite of its increased burden. The method by which Sussman, Steinberg and Grishman<sup>32</sup> could inject a radiopaque substance into the blood stream and then under the fluoroscope study the action of the different chambers of the heart in various diseases, notably in emphysema, is illuminating. Their article contains a series of handsome photographs and diagrams.

26 Friedberg, S. A. Bronchoscopy and Asthmatic Respiration, *J. A. M. A.* **123** 85 (Sept. 11) 1943.

27 Bases, L., and Kurtin, A. Prevention of Death in Status Asthmaticus. Value of Bronchoscopy, *Arch. Otolaryng.* **36** 79 (July) 1942.

28 Osgood, H. Blood Pressure Fluctuations in Respiratory Obstruction, *J. Lab. & Clin. Med.* **27** 1536, 1942.

29 Osgood, H. Blood Pressure Fluctuations in Bronchial Asthma, *J. Lab. & Clin. Med.* **28** 927, 1943.

30 Vaccarezza, R. F., and Cucchiari Acevedo, R. Artificial Pneumothorax in Pulmonary Tuberculosis Complicating Asthma, *An. Cated. de pat. y clin. tuberc.* **3** 67, 1941.

31 Schiller, W., Colmes, A., and Davis, D. The Occurrence of Cor Pulmonale in Cases of Bronchial Asthma, *New England J. Med.* **228** 113, 1943.

32 Sussman, M. L., Steinberg, M. F., and Grishman, A. Contrast Visualization of Heart and Great Vessels in Emphysema, *Am. J. Roentgenol.* **47** 368, 1942.

*Periarteritis Nodosa*—In July 1942 Rich,<sup>33</sup> of Baltimore, submitted an important paper in which he gives evidence that periarteritis nodosa is a part of serum disease. Rich points out that, whereas deaths from serum disease are extremely rare, the use of sulfonamide drugs has prolonged life so as to permit serum disease to develop before death. He collected 6 cases in which the patients died during serum disease and another case in which a biopsy of muscle taken during serum disease showed similar lesions. In addition, Rich recalls that Clark and Kaplan<sup>34</sup> in 1937 had found 2 patients who had died during serum disease. In 2 cases of Clark and Kaplan and in the seventh case in his own series there had been no treatment with sulfonamide drugs. In each of these 9 cases autopsy showed the familiar lesions of periarteritis nodosa, necrosis of the walls of the blood vessels and fibrinoid alteration, with hyalinization later, all associated with local hemorrhages as well as with local eosinophilia. Were these lesions due to the disease, to the serum or to the drug? The fact that 3 patients had not received any sulfonamide drug rules out the last possibility, and, furthermore, in 1 case a maculopapular rash, different from the urticaria, had appeared with the beginning of treatment with the drug and subsided when it was discontinued and before the urticaria had appeared. The vascular lesions were fresh. As for the disease factor, the very fact that periarteritis nodosa should have occurred in several different diseases when it was not a part of the ordinary pathologic process of those diseases makes it almost sure that its development depended on the serum.

In a second paper, submitted in November 1942, Rich and Gregory<sup>35</sup> describe how the lesions of periarteritis nodosa could be reproduced in rabbits. Fourteen animals received horse serum in doses of 10 cc per kilogram of body weight, and 5 of them received sulfadiazine in addition. Most of the rabbits acquired the flush which Fleischer and Jones<sup>36</sup> had described as

the counterpart of serum disease in rabbits. On the twelfth day skin tests showed all the rabbits to be sensitized, and on the seventeenth day all were reinoculated, with 1 cc of horse serum. However, only 2 of the animals died. After that some of the animals were killed and others were reinoculated with horse serum in different amounts at different intervals. When these animals were killed and autopsies were performed, every state of periarteritis nodosa could be demonstrated in the blood vessels. The endothelium was damaged, fluid and inflammatory cells appeared in the adventitia and the muscle became hyalinized and necrotic later.

It is important that Rich and Gregory could produce these lesions in rabbits by treatment with horse serum alone. Indeed they showed that the lesions could result from a single large injection of horse serum. Sulfadiazine did not play any direct part in producing the typical pathologic pictures.

Baker<sup>37</sup> reports 2 cases of periarteritis nodosa, and gives an extensive description of the clinical, laboratory and pathologic observations. The first case was that of a man aged 39 who had had severe asthma for two years. About a year before his death pain and swelling suddenly developed in the legs, and later came other swellings and purpuric spots. The first blood counts showed only 5 to 8 per cent of eosinophils, but toward the end his white cell count rose to 25,000 and the eosinophils to 70 per cent. At autopsy the vessels in all the organs showed periaarterial infiltration with fibrosis. The second patient was a man aged 47 admitted to the hospital because of fever, weakness and bodily pains of about one week's duration. He lived for five months and during that time had a progressively downhill course. Peripheral neuritis developed, and also a progressive retinitis. Petechial hemorrhages appeared at the end, and he died of heart failure. At no time did he have any asthma or any other symptoms of allergy. His white cell count rose only to 15,000, and the proportion of eosinophils was never above 2 per cent. Autopsy was refused, but a biopsy of the gastrocnemius muscle showed extensive periaarterial lesions with fibrous proliferation, numbers of lymphocytes and scattered eosinophils. In the media of the larger arterioles were collections of pale cells forming pseudotubercles. (Giant cells have been described by other pathologists.) These cases are summarized here in order to emphasize that whereas periarteritis nodosa occurs in patients

33 Rich, A. R. The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, *Bull Johns Hopkins Hosp* **71** 123, 1942.

34 Clark, E., and Kaplan, B. I. Endocardial, Arterial and Other Mesenchymal Alterations Associated with Serum Disease in Man, *Arch Path* **24** 458 (Oct) 1937.

35 Rich, A. R., and Gregory, J. E. The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, *Bull Johns Hopkins Hosp* **72** 65, 1943.

36 Fleischer, M. S., and Jones, L. R. Serum Sickness in Rabbits. I. Manifestations of Serum Sickness, *J Exper Med* **54** 597, 1931.

37 Baker, L. A. Periarteritis Nodosa, with Report of Two Cases, *Ann Int Med* **17** 223, 1942.



with severe asthma, it may occur also in other conditions

Important is a recent paper by Selye and Pentz,<sup>38a</sup> who have carried the study much further. They point out that the lesions of periarteritis nodosa are similar histologically to the arterial lesions in the kidneys of patients with malignant hypertension and are reminiscent of rheumatic foci (Rheumatic fever and periarteritis nodosa occur together with some frequency). They also point out that the lesions of periarteritis nodosa have been produced by treatment with a number of different substances, by injections of various proteins, by injection of streptococci and by feeding a high protein diet to unilaterally nephrectomized rats. "Nephrotoxic" serums are often described. Selye and Pentz found that certain steroid hormones were potent in producing nephrosclerosis and that at the same time extrarenal vessels were often damaged by these hormones. Rats were given extra salt in their diet, and then some of the animals had one kidney removed. When the animals were treated with desoxycoiticosterone acetate the lesions were produced (more in the group operated on), and the photographs which accompany the paper show the typical changes of periarteritis nodosa. The authors explain that a sudden stress, such as cold, fatigue or infection, may elicit the "alarm reaction," and "if the damaging stimulus continues, it is followed by the resistant stage and eventually by the exhaustion stage of the general adaptation syndrome.

It has been found that exposure to cold or other damaging agents causes rats sensitized by salt treatment, unilateral nephrectomy or preferably both to have pathologic changes identical with those produced by administration of desoxycoiticosterone acetate."<sup>38b</sup> During this process the adrenal cortex increases in size and produces excessive amounts of its hormone. Meantime, body proteins break down or perhaps foreign proteins are injected, and lesions result. The fact that acute infections, nervous shock, exposure to cold (and, I can add, repeated attacks of asthma) are sometimes followed by periarteritis nodosa or nephrosclerosis or rheumatic fever indicates that these conditions are diseases of adaptation dependent on an abnormal adaptive response of the adrenal cortex. It is an interesting conception, and it is based on what appears to be good experimental observation and evidence.

38 (a) Selye, H., and Pentz, E. I. Pathogenetical Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, *Canad. M. A. J.* 49: 264, 1943. (b) Selye, H. Unpublished communication.

From all this it is clear that periarteritis nodosa is not a disease—it is only a lesion which develops from a variety of causes and in a number of different diseases. Furthermore, it does not point to any particular specific exciting factor.

*Treatment of Asthma*—Since 1934 Barach<sup>39</sup> has been recommending the use of helium-oxygen mixtures administered by inhalation to relieve the severe paroxysms of asthma. He has now developed a plan of "bronchial relaxation," as he calls it, which in his hands at least is successful. When the patient is first admitted to the hospital, theophylline ethylenediamine is given by rectum at once—0.5 Gm in 20 cc of water. A strong (1:100) solution of epinephrine hydrochloride is used as a spray to be inhaled through the nose and/or mouth from a special atomizer connected with an oxygen tank. Dihydromorphine hydrochloride in doses of 1 or 2 mg is given subcutaneously if necessary. Finally a gas mixture containing 20 per cent oxygen and 80 per cent helium is administered by inhalation through a special apparatus. The first dose of potassium iodide (1 cc of the saturated solution in water) is also given early. The inhalation of the helium-oxygen mixture is continued for two hours in the average case, but it may be continued for twelve hours or given intermittently, according to the need. When the patient improves and becomes ambulatory, he reports to the clinic for treatment, and if he still has asthma theophylline ethylenediamine is again given by rectum, the epinephrine spray is repeated and he inhales the helium-oxygen mixture, 7 to 9 liters per minute, for about an hour. This treatment produces "bronchial relaxation" and is repeated every day for five days as indicated.

The immediate results of this treatment are good. In the hospital there were 26 patients who received 46 courses of treatment. After 34 of the courses the asthma disappeared, and only three courses were ineffective. There were 45 ambulatory patients who received 54 courses of treatment. The asthma disappeared after 23 of these courses, and only 14 were ineffective. The long term results were likewise good. Relief lasted from one to four weeks in 36 of 57 patients who were followed. It lasted from one to four months in 20 patients, from five to twelve months in 20 and for over a year in 15. Segel<sup>40</sup>

39 Barach, A. L. Repeated Bronchial Relaxation in the Treatment of Intractable Asthma, *J. Allergy* 14: 296, 1943.

40 Segel, M. S. Inhalational Therapy in the Treatment of Serious Respiratory Disease, *New England J. Med.* 229: 235, 1943.

has tried the method on 4 patients, 1 died, but the other 3 did well

Westcott and Gillson<sup>41</sup> did not use Barach's method in full, but at least they agree that inhalation of a strong (1:100) solution of epinephrine hydrochloride does good. Their paper, however, lays stress on the importance of breathing exercises, which they say can produce a substantial increase in the vital capacity and which will ultimately lead to a considerable relief of the asthma.

More recently Lockey<sup>42</sup> has tried to overcome the disadvantages of the strong (1:100) epinephrine hydrochloride solution spray, which he says tends to dry the throat and to produce palpitations and "jitters" in certain patients. He adds glycerin, hydrochloric acid, sodium chloride, chlorobutanol and sodium bisulfite to the epinephrine hydrochloride solution and claims that his prescription is less irritating.

Literature on drug treatment includes a number of new suggestions. The status of theophylline ethylenediamine and of related xanthine derivatives has been reviewed by Boyer<sup>43</sup>. Ethylenediamine is added to theophylline because the double salt is more soluble. The effect, however, depends on the xanthine compound. This is a diuretic, it increases the contraction of the heart muscle, and it can relieve Cheyne-Stokes breathing. Macht and Ting<sup>44</sup> showed that theobromine dilates the excised bronchi. Young and Gilbert<sup>45</sup> found that it has a protective effect against histamine. Whatever the mechanism, theophylline ethylenediamine is clinically useful in asthma. Dees<sup>46</sup> has found that suppositories of this compound are good.

Maietta<sup>47</sup> found that doses given intramuscularly at intervals of four to six hours were helpful to

Ether in oil is now available in ampules containing 1 cc of ether with 1 cc of peanut oil

41 Westcott, F. H., and Gillson, R. E. The Treatment of Bronchial Asthma by Inhalation Therapy with Vital Capacity Studies, *J. Allergy* **14** 420, 1943

42 Lockey, S. D. Inhalation of Oxygen and 1:100 Epinephrine Hydrochloride Plus Five per Cent Glycerin for the Relief of Asthmatic Attacks, *J. Allergy* **14** 382, 1943

43 Boyer, N. H. Aminophylline and Related Xanthine Derivatives. Present Status of Therapeutic Claims, *J. A. M. A.* **122** 306 (May 29) 1943

44 Macht, D. J., and Ting, G.-C. A Study of Antispasmodic Drugs on the Bronchus, *J. Pharmacol. & Exper. Therap.* **18** 373, 1921

45 Young, R. H., and Gilbert, R. P. The Use of Theophylline with Ethylenediamine (Aminophyllin) for the Control of Bronchial Spasm, *J. Allergy* **12** 235, 1941

46 Dees, S. C. The Use of Aminophylline Rectal Suppositories in the Treatment of Bronchial Asthma. Preliminary Report, *J. Allergy* **14** 492, 1943

patients with severe status asthmaticus. Paraldehyde is a powerful sedative, the effect of which is often immediate, so that after receiving a dose of 1 or 2 cc by mouth the patient relaxes within five minutes. Burstein<sup>48</sup> warns that there is danger in giving too much paraldehyde. The injection of as much as 30 cc by rectum caused the death of a young woman. Another patient received 15 cc in two doses six hours apart with no effect but three hours after the third dose she died. These amounts, however, are much too large. In the ordinary case, 1 or 2 teaspoons of paraldehyde (4 to 8 cc) given by mouth is sufficient to produce a dozey sleep, and in any one night 2 teaspoons are all that is required in most cases.

Nicotinic acid has been suggested for use in treatment. Suranyi<sup>49</sup> gave it to allergic children in doses of 25 or 50 mg twice a day. The effect of nicotinic acid is somewhat similar to the effect of histamine, and doses given by mouth are often followed by the appearance of erythema and a feeling of heat and warmth. Urticaria, asthma and spastic bronchitis were found to respond favorably. The drug is said to be useful for certain types of headache, as will be discussed. Nicotinic acid is a vasodilator drug.

Nucleic acid is used by Howe<sup>50</sup> in the treatment of subacute and chronic sinusitis with the idea that the condition depends either on a deficiency of nucleoproteins in the diet or on faulty absorption of these substances. So far, however, there is not much evidence to support either of these theories. Potassium salts have been advised for some years. Carlson and Whitehead<sup>51</sup> review the literature. They found that the feeding of sodium salts to guinea pigs suffering from anaphylactic shock had no protective effect but that potassium salts could save the animals from death.

Sulfonamide drugs have been advocated for the treatment of asthma, as might be expected. Jiménez-Díaz and his co-workers<sup>52</sup> gave sulfa-

47 Maietta, A. L. The Use of Ether in Oil Intramuscularly in the Treatment of Bronchial Asthma, *New England J. Med.* **227** 985, 1942

48 Burstein, C. L. The Hazard of Paraldehyde Administration. Clinical and Laboratory Studies, *J. A. M. A.* **121** 187 (Jan 16) 1943

49 Suranyi, J. Suggestion for Treatment of Allergic Conditions, *Ann. pædiat.* **158** 231, 1942

50 Howe, A. C. Nucleic Acid Treatment of Subacute and Chronic Sinusitis, *Ann. Otol., Rhin. & Laryng.* **51** 220, 1942

51 Carlson, R. G., and Whitehead, R. W. The Effect of Sodium, Potassium, and Thiosulfate Ions on Anaphylaxis, *J. Allergy* **14** 462, 1943

52 Jiménez-Díaz, C., Lahoz, C., and Recatero, L. Sulfapyridine Therapy of Persistent Bacterial Asthmas, *Rev. clin. españ.* **4** 423, 1942



pyridine to 10 patients with status asthmaticus, and in 8 of them the therapy effected a disappearance of all symptoms. The authors' explanation is that bacterial infection played an important part. My associates and I have tried sulfonamide compounds in a few cases, but our results have not been good, and there is always the danger of producing another specific sensitiveness to complicate the picture.

Last winter the laity read about a new treatment for asthma described in the daily press. Some editor was intrigued by Lapp's<sup>53</sup> claim that small doses of the patient's own serum can be given at regular intervals to produce a "desensitization" and cure his asthma. The idea is not new. It developed originally from the conception that the causative antigen is absorbed into the blood stream and that the blood can be assumed to contain it even though its nature is unidentified. Originally the method was to defibrinate the blood and then reinject a relatively large quantity, perhaps 20 to 50 cc, into the muscle. A simpler method is to draw blood from a vein of the arm and then, while it is still "hot" and uncoagulated, to inject it immediately, with the same needle and syringe, into the buttock. The procedure is somewhat dramatic, and it is a little painful. More important, it carries the considerable danger that the pool of blood that is produced at the site of the injection may become infected. I doubt if the method has much more than a psychologic value, but in some cases this appears to be considerable.

There are several new methods for making the absorption of injected drugs slow and prolonged. Abramson and Arsenal<sup>54</sup> add gelatin to epinephrine. Spain and his co-workers<sup>55</sup> recommend gelatin as a vehicle for ragweed pollen extract. In order to reduce the power of jelling and to make the material less viscous, they treated the gelatin solution in the autoclave at 20 pounds' (9 Kg) pressure for one and three-quarters hours. The gelatin hydrolyzed and as such was added to the strong pollen extract to make the gelatin-pollen mixture. With this material 28 of 55 patients had little or no hay fever, whereas with the ordinary watery pollen extract only 14 of 55 patients had really good results. Nater-

man<sup>56</sup> uses epinephrine base suspended in an aqueous solution of sodium thioglycolate, which is an acid-reducing agent and so prevents the epinephrine base from being oxidized too rapidly.

Suspensions of epinephrine base in oil have been studied by Richards<sup>57</sup>. In experiments on rats he found that the toxicity of the preparations was the same as that of aqueous solutions of epinephrine hydrochloride. Furthermore, experiments designed to demonstrate a more prolonged action of the oil mixture by means of blood sugar curves did not give any impressive result. When the size of the particles was reduced by special grinding, the toxicity was less, possibly because the small particles were better protected by a film of oil, which delayed their absorption.

Oil has been used to delay the absorption of pollen. Taub and Rubens<sup>58</sup> made a 3 per cent extract of pollen in water and then evaporated it to dryness under vacuum. This lyophilized pollen was then homogenized electrically into sterile sesame oil. When this material was used for skin tests the positive reaction was delayed for about thirty minutes in its appearance.

Meantime, Foldes<sup>59</sup> has worked with a different principle in trying to prolong the action of subcutaneously injected medicaments. He recalled that certain metals can prolong the action of injected drugs, and so he used zinc chloride in concentrations of 0.1 per cent or less. With posterior pituitary extract, the antidiuretic action is much prolonged. When zinc chloride was added to epinephrine hydrochloride solution, the mobilization of blood sugar was delayed to a definite degree. In another experiment he tried his "zinc-epinephrine" solution on a patient with asthma. There was no delay in the onset of the antiasthmatic effect, but he observed that the effect lasted for six to eight hours instead of the usual three to four hours. The plan deserves further study.

Finally, a paragraph from a recent paper by Sir Arthur Hurst<sup>60</sup> is copied in full. "Every

53 Lapp, A. D. Asthma Treated with Patient's Blood Serum, *Brit. M. J.* **1** 552, 1942.

54 Abramson, H. A., and Arsenal, E. A U.S.P. Gelatin Vehicle in Liquid Form for Retardation of Absorption with Special Reference to Epinephrine, *J. Allergy* **14** 414, 1943.

55 Spain, W. C., Fuchs, A. M., and Strauss, M. B. The Treatment of Hay Fever with Gelatin-Pollen Extracts, *J. Allergy* **14** 376, 1943.

56 Naterman, H. L. Adrenalin Base Suspended in an Aqueous Solution of Sodium Thioglycolate in the Treatment of Asthma, *New England J. Med.* **227** 736, 1942.

57 Richards, R. K. A Pharmacologic Study of Epinephrine Suspensions in Oil, *J. Allergy* **14** 177, 1943.

58 Taub, S. J., and Rubens, E. Pollen Oil. A Preliminary Report on a New, Slowly Absorbed Medium for the Use in Hay Fever Treatment, *Ann. Int. Med.* **17** 642, 1942.

59 Foldes, F. F. The Prolongation of the Action of Subcutaneously Injected Medicines in Man, *J. Clin. Investigation* **22** 499, 1943.

60 Hurst, A. Asthma in Childhood, *Brit. M. J.* **1** 403, 1943.

asthmatic can derive much benefit from good advice. He can be taught a way of life, how to avoid the exciting causes of his particular brand of asthma, how to control attacks he is unable to prevent, and above all, how to be happy in spite of the bad luck of having been born with the asthma diathesis."

Results of treatment are not often described. Unger and Wolf<sup>61</sup> describe the status of 207 patients followed for seven years or more after the first treatment. Those who were free of symptoms continued well, and of 104 previously reported as improved, 19 were free of asthma. Another 252 patients have been added to the study, to make a total of 459. Of these, 298, or 65 per cent, had "paroxysmal asthma" and 93 were well, whereas only 4 of 161 patients with chronic persistent asthma were free of symptoms. Best results were obtained in patients whose paroxysmal asthma was caused by some allergen which could be found and eliminated. These are the persons who began to have asthma early in life. Forty-eight patients had died, the asthma was the main cause of death of 21, and the contributing cause for 16. Morphine was known to have been given just prior to death to 6 patients. Presumably these were patients whose asthma began late in life (after the age of 45) and who therefore had quite a different disease from those whose asthma began before the age of 30. In any study of end results in asthma the clinical classification of the patient is of primary importance.

Describing the results of operations on the sinuses in cases of chronic infection, after an interval of two to eight years, Cooke<sup>62</sup> reports that of 74 patients operated on 52 per cent have had little or no asthma and only 8 are not improved, but of 78 patients that were not operated on only 13 per cent have been relieved and 64 are not improved. Needless to say, he lays stress on the selection of cases and on the technic of operating. (Such results cannot be obtained in my clinic.)

#### CHEMICAL EFFECTORS

The mechanism by which asthma and the other manifestations of hypersensitiveness are produced is not at all clear, but the study of the problem still centers around the chemical effectors—the powerful substances which are normally present in the body and which are released by various

exciting factors. Nerve impulses exert their effect through the effectors, especially acetylcholine, whereas direct stimulation, as by injury or perhaps by antigen-antibody reactions on the surface of cells, causes the release of histamine from those cells.

When antigen is mixed with sensitive blood *in vitro*, histamine is released from the cells and can be found in the plasma. Dragstedt, Wells and Rocha e Silva<sup>63</sup> found that when heparin was added to the blood to prevent clotting the quantity of histamine released was less than without heparin. Furthermore, this inhibition was about the same whether sensitive blood was treated with antigen or whether normal blood was treated with trypsin or peptone. This is further evidence that the mechanism of peptone shock is not different from that of anaphylactic shock. In another experiment, Dragstedt<sup>64</sup> treated a large number of dogs with peptone, 10 per cent Bacto-peptone (Difco) in doses of 2 cc per kilogram. The primary injection often caused severe reactions, but in some of the dogs it was possible to raise the resistance to subsequent doses. Refractoriness to peptone cannot, however, be effected without inducing shock, and the degree of resistance is determined usually by the severity of that shock. Dragstedt found a good deal of crossed relationship between shock of different kinds. Animals made refractory to Witte's peptone, derived from fibrin, were refractory to Armour's peptone, made from milk. The relation between peptone shock and anaphylactic shock was fairly close. When mild anaphylactic shock was induced in sensitized dogs, a subsequent dose of peptone caused a severe reaction in over half the animals. When, however, the anaphylactic shock was more severe, only 3 of the 13 animals reacted severely to the subsequent dose of peptone. Refractoriness to peptone has nothing to do with the binding of antigen to antibody; it is concerned chiefly with the reaction itself, that is, with the release of the chemical effector. Essex and Horton<sup>65</sup> were able to increase the resistance of guinea pigs to histamine to some extent by treating their animals with histamine in small subcutaneous doses. Of the pretreated animals,

63 Dragstedt, C. A., Wells, J. A., and Rocha e Silva, M. Inhibitory Effect of Heparin upon Histamine Release by Trypsin, Antigen and Protease, *Proc Soc Exper Biol & Med* **51** 191, 1942.

64 Dragstedt, C. A. Observations on Spontaneous and Induced Refractoriness to Peptone Shock in Dogs, *J Immunol* **47** 1, 1943.

65 Essex, H. E., and Horton, B. T. Observations on Development of Resistance to Histamine in the Guinea Pig, *Proc Staff Meet, Mayo Clin* **16** 603, 1941.

61 Unger, L., and Wolf, A. A. Treatment of Bronchial Asthma. A Survey of the Value of Treatment in Four Hundred and Fifty-Nine Cases During Twenty Years, *J A M A* **121** 325 (Jan 30) 1943.

62 Cooke, R. A. The Practitioner and the Allergy Problem, with Special Reference to Respiratory Allergy, *Rhode Island M J* **25** 152, 1942.

27, or 41 per cent, survived the lethal dose, as compared with only 5 per cent of the controls

Thyroid depletes the stores of ascorbic acid and cholesterol in the adrenal glands. According to Farmer and Fribourg<sup>66</sup> this results in a depletion of the cortical hormone, and this in turn produces an increase in sensitiveness to histamine. Animals fed thyroid for several days were more susceptible to histamine than were the untreated controls.

Wilcox and Seegal<sup>67</sup> found an ethylenediamine derivative which would protect guinea pigs against 1 to 6 minimal lethal doses of histamine although cyanosis and prostration without death occurred in many animals. They believed that the drug acted primarily to prevent contraction of the smooth muscle but not to prevent the development of other manifestations of shock. Courtright. Hurwitz and Courtright<sup>68</sup> produced anaphylactic shock by exposing guinea pigs sensitive to horse dander to inhalation of the specific dust, and he tried to protect them by treatment with histamine and with acetylcholine as well as with histaminase. Even though the doses and intervals were varied considerably, he was unable to demonstrate any definite preventive action by any one of the three substances.

Histamine in the treatment of clinical allergy has been recommended. Farmer and Kaufman<sup>69</sup> gave histamine subcutaneously increasing the doses at frequent intervals, for the treatment of chronic vasomotor rhinitis as well as of hay fever. In 41 cases of perennial rhinitis, the results were good in 25 instances, fair in 10 and poor in 6. In 24 cases of severe ragweed hay fever, the results were good in 7 and fair in 9. In 48 cases of moderate ragweed hay fever, the results were good in 19 and fair in 13, and in 15 cases of grass hay fever, the results were good in 9 and fair in 6. The result of treatment was better in the cases of perennial rhinitis. More recently,

66 Farmer, L, and Fribourg, R. Studies on Histamine Sensitivity and Anaphylactic Response. The Effect of Thyroid Extract, *Proc Soc Exper Biol & Med* **50** 208, 1942.

67 Wilcox, H B, Jr, and Seegal, B C. Influence of an Ethylenediamine Derivative on Histamine Intoxication and Anaphylactic Shock in the Intact Guinea Pig and Isolated Guinea Pig Heart, *J Immunol* **44** 219, 1942.

68 Courtright, L J, Hurwitz, S H, and Courtright, A B. Inhalant Sensitization and Shock in Guinea Pigs Under Controlled Atmospheric Conditions. II. Histamine, Histaminase, and Acetylcholine as Possible Preventives, *J Allergy* **13** 444, 1942.

69 Farmer, L, and Kaufman, R E. Histamine in the Treatment of Nasal Allergy (Perennial and Seasonal Allergic Rhinitis), *Laryngoscope* **52** 255, 1942.

Gant, Savignac and Hochwald<sup>70</sup> have given histamine by mouth, for treatment of chronic vasomotor rhinitis. They find that the drug is absorbed rapidly from the gastrointestinal tract and that when the patient starts with a small dose, perhaps with 1 drop of a 1:10,000 dilution of histamine in water, and then increases the amount by slow, careful increments, a dose is soon found which causes a sense of warmth and flushing of the skin, and when this occurs the nasal symptoms improve. The size of that dose is noted carefully, and thereafter the same quantity is taken two or three times a day, as often as may be necessary to secure relief. The trick is to find the dose, which may vary in different cases from 1 drop of a 1:10,000 dilution (0.01 mg) to 5 drops of a 1:100 dilution (3 mg). Enough patients have been relieved by this method to justify further study of it.

Histamine in the treatment of Ménière's syndrome has been recommended for some years. Rainey<sup>71</sup> reports on 6 patients who were treated with histamine phosphate intravenously. The ampule containing 275 mg in 1 cc is diluted to 250 cc with isotonic solution of sodium chloride to make a 1:100,000 dilution of histamine phosphate. The speed of injection is important, for in some cases as much as 20 drops a minute will cause flushing and headache, while in others 70 drops a minute is borne without difficulty. After the initial intravenous treatment, further doses may be given at intervals subcutaneously. All 6 of Rainey's patients did well.

Atkinson<sup>72</sup> also uses histamine for Ménière's disease, but he has found it important to distinguish the patients whose headaches depend on vasoconstriction and whose skins are not sensitive to histamine from the other group, whose headaches depend on vasodilatation and who show an extensive reaction to histamine in a skin test. Atkinson assumes that histamine is in part responsible for the normal balance of vasodilatation against vasoconstriction. Added histamine will have an immediate vasodilator action, and the headache will be relieved, but meantime it will tend to produce an increased resistance of the body toward histamine, so that vasoconstriction will be favored. When the headache is due to

70 Gant, J, Savignac, R J, and Hochwald, A. Histamine by Mouth in the Treatment of Vasomotor Rhinitis, *New England J Med* **229** 579, 1943.

71 Rainey, J J. Histamine in the Treatment of Meniere's Syndrome, *J A M A* **122** 850 (July 24) 1943.

72 Atkinson, M. Histamine in the Treatment of Meniere's Syndrome, *J A M A* **119** 4 (May 2) 1942.

vasodilatation, this is desirable, but headaches due to vasoconstriction will be made worse. For these nicotinic acid, given in doses of 50 mg by vein at first and by mouth later, appears to be effective.

Neostigmine for treatment of headache is suggested by Pelner.<sup>73</sup> If acetylcholine is the effector which causes trouble, neostigmine, by blocking the cholinesterase, should prevent the destruction of acetylcholine and allow its absorption. Pelner found that prostigmine bromide given in doses of 15 mg by mouth produced a headache, and so he dissolved the tablet in an ounce of tap water and then prescribed drop doses of the solution by mouth. Like Atkinson, Pelner considered the finding of a positive reaction to a skin test with histamine 1:1,000 and with acetylcholine 1:20 as the necessary criterion for success. Of 46 patients, 37 were completely relieved and 5 were much improved by Pelner's treatment.

Atropine prevents the action of acetylcholine, and it is interesting to have Bender, working in Abramson's laboratory,<sup>74</sup> find that atropine could inhibit the cutaneous reactions caused by mecholyl but not the flare caused by histamine (the reactions being produced by driving the substances through the skin with an electric current).

#### ANAPHYLAXIS

Death following the injection of foreign protein is still reported, in spite of increasing knowledge of the dangers. Vance and Strassmann<sup>75</sup> collected from the records of the chief medical examiner of the city of New York the accounts of 7 necropsies. Five were of persons who died suddenly after an injection of antitoxin, and 2 were of allergic persons who were killed by specific treatment. One of these was a child who died shortly after an intracutaneous test with a mixture of silk, wool and kapok extracts. The other was an asthmatic adult who died after a routine injection of ragweed extract. In each case the lungs were greatly distended (insufflated) and the viscera were congested. From the literature the authors collected the reports of 18 similar cases. Of the total of 25 patients, all except 3 patients died within

ten minutes after the injection, and the 3 died in six hours, fourteen hours and twenty-three hours respectively. Of the total 25, only 13 had a history of any previous treatment with foreign proteins, and the authors postulate a hereditary constitutional factor in addition to anaphylaxis.

About a year ago two groups of patients in a hospital for persons with mental disease were given small doses of guinea pig serum in order to study the development of hypersensitiveness. One of them, an apparently healthy woman of 22, died within ten minutes after receiving 0.2 cc of guinea pig hemoglobin injected intradermally. At autopsy, an acute hemorrhagic inflammatory reaction was found at the site of treatment, there were edema of the upper air passages and emphysema with large pleural bullae. The case was studied by the medical examiner, Dr. Hunt.<sup>76</sup> The first question was whether the woman was actually sensitive, and an interesting experiment was made. Her serum obtained from the heart's blood was found to sensitize the skin of 3 normal recipients so that the prepared sites reacted well to solutions of guinea pig hemoglobin. The diagnosis of allergy and anaphylaxis was proved. In passing, let me observe that reactions were still demonstrable in spite of and immediately after the overwhelming reaction.

A comment on this case appeared subsequently in *The Journal of the American Medical Association*<sup>77</sup> and included the following statement: "Close inquiry disclosed that the mother of the subject of this report had asthmatic attacks and symptoms of hay fever, that a brother suffered from hay fever and that the mother's first cousin, also asthmatic, died at the age of 16, ten minutes after the subcutaneous injection of diphtheria antitoxin, the first death of that kind in this country. The lesson again brought home by the bare facts in Dr. Hunt's report is that the most watchful precaution must always be taken to avoid fatal shock on the injection of foreign protein antigenic material into human beings."

#### INDUSTRIAL DERMATITIS

Industrial dermatitis appears to be a fairly constant menace, even though the total number of cases is not large. A report of the Committee on Occupational Dermatoses of the American Medical Association, presented by Foerster and

73 Pelner, L. The Treatment of Periodic Occipital Headache with "Desensitizing" Doses of Prostigmine, *Dis Nerv System* 4:177, 1943.

74 Bender, M. B., Abramson, H. A., and Ehrlich, G. Skin Reactions. XIV The Effect of Atropine on the Mecholyl and Whealing Reactions of the Skin, *J Mt Sinai Hosp* 9:322, 1942.

75 Vance, B. M., and Strassmann, G. Sudden Death Following Injection of Foreign Protein, *Arch Path* 34:849 (Nov) 1942.

76 Hunt, E. L. Death from Allergic Shock, *New England J Med* 228:502, 1943.

77 Kortright, J. L. Practical Experiences with Antitoxin, *Brooklyn M J* 10:87, 1896.

others,<sup>78</sup> describes in some detail the methods of diagnosis, prevention and treatment. The allergic background of each employee should be studied, and attention should be paid to any neurogenic or psychogenic relationships. Habits of eating and living may need a good deal of correction.

Oil folliculitis and dermatitis are not uncommon. Cutting oils may be of animal, vegetable or mineral composition, and the prevention of the dermatitis which may follow their use is chiefly a matter of personal cleanliness, the achievement of which can be facilitated by adequate provision for washing hands, body and clothes. Sulfonated oils are produced by treating natural oils with sulfuric acid and then neutralizing the excess acid with an alkali. Some of these preparations mix well with water to form creamy emulsions and become useful as cleansing agents. The new development of "soapless soap" depends primarily on the use of sulfonated oils of one sort or another. Occasionally, however, trouble may come from these preparations.

Zinc dermatitis is described by Freeman<sup>79</sup> as a hazard in the aircraft industries, where certain alloys are used. Patch tests with zinc elicit positive reactions in the victim and quite negative reactions in controls. Sodium chlorate and sodium dichromate are encountered in the production of air-conditioning equipment. Schwartz and Dunn<sup>80</sup> found that 14 per cent of 105 workers had dermatitis which could be attributed to that cause. Sodium dichromate is also used as a wetting agent for the dyes employed in the manufacture of blankets for the Army, and the same authors<sup>81</sup> found trouble in this group of workers also. Dermatitis due to resin finishes for cotton fabrics, especially underwear, has been described by Keil<sup>82</sup> and also by Costello and Ryan,<sup>83</sup> the latter reporting

on 20 cases which were observed at the Bellevue Hospital in New York.

Dhobie is a nut tree in India. Its sap turns black and so makes a convenient fluid for marking clothes. Goldsmith<sup>84</sup> found that the soldiers developed a dermatitis under the neck band or at the waist where the marks touched the skin. It was difficult to get rid of the sensitizing effect of the marks. Boiling of the clothes was ineffective. Dermatitis of the face from contact with the rubber parts of gas masks is described by Petro,<sup>85</sup> who demonstrated positive reactions to patch tests with the "accelerator" and the "antioxidant" used in the manufacture of that particular rubber. Fox<sup>86</sup> describes a farmer who became sensitive to the dust of mesquite wood. Patch tests with the ether extract of the sawdust produced a positive reaction. Contact dermatitis from cod liver oil is described by Cope.<sup>87</sup>

Cosmetics still hold an important place in the list of causes of contact dermatitis. Simon<sup>88</sup> observed 13 patients with eczema of the face who gave positive reactions to patch tests with five different brands of nail lacquer, both colorless and colored. After avoidance of the lacquer 11 of the 13 patients were cured at once. Patch tests made with a variety of different ingredients showed reactions to a certain formaldehyde-sulfonamide resin which was used in making the lacquer. More recent are reports by Howell<sup>89</sup> and by Epstein<sup>90</sup> describing contact dermatitis from hair lacquer, a new preparation and evidently an important feature of the latest "up-do" coiffure.

As has been said elsewhere, it is evident that the list of substances capable of producing local reactions on the human skin is never complete, especially in this modern day when chemicals, both old and new, are being used more and more even in what appear to be fairly simple and clean processes.

78 Foerster, H. R., and others. Recognition and Prevention of Industrial Dermatitis, with Additional Reference to Oil Dermatitis and Folliculitis. A Report of the Committee on Occupational Dermatoses, American Medical Association, J. A. M. A. **122** 370 (June 5) 1943.

79 Freeman, H. E. Zinc Dermatitis. An Additional Hazard in Aircraft Industries, J. A. M. A. **119** 1016 (July 25) 1942.

80 Schwartz, L., and Dunn, J. E. Dermatitis Occurring Among Operators of Air-Conditioning Equipment, Indust. Med. **11** 375, 1942.

81 Schwartz, L., and Dunn, J. E. Dermatitis Occurring in a Woolen Mill, Indust. Med. **11** 432, 1942.

82 Keil, H. Dermatitis Due to Resin-Finished Shorts and Fabrics, J. Allergy **14** 477, 1943.

83 Costello, M. J., and Ryan, J. E. Dermatitis from Underwear Shorts Processed by Resin Finishes. Report of Twenty Cases Observed at Bellevue Hospital, Arch. Dermat. & Syph. **46** 254 (Aug.) 1942.

84 Goldsmith, N. R. Dermatitis from Semecarpus Anacardium (Bluelawanol or the Marking Nut), J. A. M. A. **123** 27 (Sept. 4) 1943.

85 Petro, J. Respirator Dermatitis, Brit. M. J. **1** 631, 1942.

86 Fox, E. C. Mesquite Wood Dermatitis, Arch. Derm. & Syph. **44** 1098 (Dec.) 1941.

87 Cope, E. P. Contact Dermatitis Due to Cod Liver Oil. Report of a Case, Arch. Dermat. & Syph. **46** 140 (July) 1942.

88 Simon, F. A. Nail Polish Eczema, South. M. J. **36** 157, 1943.

89 Howell, J. B. Contact Dermatitis from Hair Lacquer, J. A. M. A. **123** 408 (Oct. 16) 1943.

90 Epstein, S. Contact Dermatitis Caused by Hair Lacquer Pads. A Characteristic Clinical Picture, J. A. M. A. **123** 409 (Oct. 16) 1943.



Stokes gave a lecture<sup>91</sup> full of common sense and good advice to Army surgeons on infections of the hands and feet and referred particularly to the dermatitis which certain surgeons acquire from certain kinds of rubber gloves. He recommended huge doses of D G A D (Don't give a damn), "that psychologic soporific which reduces the eternal friction between what one feels he must do and what one thinks he can." In other words, he felt that tension, fatigue and "poor condition" were aggravating factors even of a local disease like contact dermatitis.

#### GENERALIZED CUTANEOUS REACTIONS, DRUG ALLERGY

Of greater and more exciting interest, if not of more practical importance, is a group of cases in which drugs have caused generalized symptoms of all sorts. These reactions have been reviewed repeatedly, but the literature still contains reports of new cases due to new drugs or combinations of drugs. Barefoot and Callaway<sup>92</sup> give an excellent review of the literature on barbitol poisoning. The barbiturates were introduced in 1913, and during the first fifteen years of their use only 41 instances of untoward reaction were found in the literature. In the second fifteen year period, however, the authors find 13 cases of exfoliative dermatitis due to phenobarbital, of which 10 were fatal. Their own case which they describe illustrates the unusual occurrence of trouble after relatively small doses of phenobarbital. A woman of 58 had taken only 32 mg ( $\frac{1}{2}$  grain) of phenobarbital three times a day, and only for ten days, before her face became "sunburned." The next day her whole skin became red, and a week later it began to exfoliate. She stayed in the hospital for thirty-five days before she could be discharged as well. A month later she took exactly 1 pill of phenobarbital and the next day she became red and soon went through the whole illness all over again, her skin desquamating completely. As the authors say, she is now convinced that phenobarbital is not good for her!

Thomas and Fenton<sup>93</sup> describe 9 cases in which pontocaine, used locally for bronchoscopy in 4 instances, for tooth extraction in 1 and for

gastrosocopy in 4, produced extremely severe reactions, which were fatal in 3 of the cases. After that experience use of pontocaine was discontinued at the Cleveland Clinic.

Diethylstilbestrol can cause trouble. Kasselberg<sup>94</sup> reports on a patient in whom generalized exfoliative dermatitis developed after the last of three weekly doses of the drug. Later skin tests elicited a strong immediate reaction with pseudopod formation. Saphir and Weinglass<sup>95</sup> write of a case in which a woman received 0.5 mg of diethylstilbestrol each night and after five days pitting edema of both hands developed and then edema of the face and neck with laryngeal stridor. In this case, too, a skin test with a 1:2,000 dilution of diethylstilbestrol in water resulted in a tremendous immediate local urticarial reaction. Amphetamine sulfate caused a severe toxic reaction in a patient described by Kauvar, Henschel and Ravin<sup>96</sup>. In this case the reactions to skin tests were negative.

Saunders<sup>97</sup> reports his own experience of trouble from inhaling dry powdered neoarsphenamine. For some years he had been opening ampules to prepare solutions for his patients, and recently he found that within a minute or two he began to sneeze and his nose began to run. Skin tests made even by the scratch method with a 6 per cent solution of neoarsphenamine caused not only an extensive local reaction but in a few moments a general reaction with asthma—evidently analogous to the general reactions which occur from time to time in the treatment of any large group of patients with hay fever.

Two cases of sensitivity to quinine are reported by Rose<sup>98</sup>. In both patients a generalized erythematous eruption with swelling of the genitals developed after ingestion of 2 tablets of quinine bisulfate. Previously both patients had suffered reactions of the genitals following the use of contraceptives.

Diodrast is an iodine compound used freely in making roentgen studies of the renal pelvis

91 Stokes, J. H., and Lee, W. E. Contact, Contact-Infective and Infective-Allergic Dermatitis of the Hands, *J. A. M. A.* **123** 195 (Sept 25) 1943.

92 Barefoot, S. W., and Callaway, J. L. Exfoliative Dermatitis Due to Phenobarbital. Report of a Case with Recovery, *Ann. Int. Med.* **18** 105, 1943.

93 Thomas, J. W., and Fenton, M. M. Fatalities and Constitutional Reactions Following the Use of Pontocaine, *J. Allergy* **14** 145, 1943.

94 Kasselberg, L. A. Case of Exfoliative Dermatitis Due to Diethylstilbestrol, *J. A. M. A.* **120** 117 (Sept 12) 1942.

95 Saphir, W., and Weinglass, A. R. Severe Angio-neurotic Edema Following Diethylstilbestrol Therapy, *J. A. M. A.* **119** 557 (June 13) 1942.

96 Kauvar, S. S., Henschel, E. J., and Ravin, A. Toxic Eruption Due to Amphetamine Sulfate and Its Analogue Dextroamphetamine Sulfate, *J. A. M. A.* **122** 1073 (Aug 14) 1943.

97 Saunders, T. S. Respiratory Allergy from the Arsphenamines. Personal Case Report, *J. Allergy* **14** 76, 1942.

98 Rose, M. M. Two Cases of Quinine Sensitivity, *M. J. Australia* **1** 71, 1943.

Reactions to diodrast based on a sensitivity to the substance are not as uncommon as expected. In my review of the literature of 1942<sup>99</sup> I commented on several reports of reactions to diodrast. Other reports are noted this year, the subject is evidently important. Last winter at the Massachusetts General Hospital a woman of 45 stopped breathing and became cyanotic within a minute or two after an intravenous injection of diodrast had begun. For a few moments her condition was precarious, but epinephrine was injected at once and she recovered. She had a chronic pyelitis, and roentgen studies with use of diodrast had been made before. She recalled that she had felt chilly and weak after the last two examinations. How often does diodrast cause slight symptoms? Evidently they are easy to overlook. In this case no one appreciated that the patient might have become sensitized by the previous treatment. No one asked about previous reactions. Archer and Harris<sup>100</sup> say that instillation of a drop of diodrast solution into the eye is an easy test for sensitiveness which has proved effective in over 600 unselected cases. Robins<sup>101</sup> made skin tests with diodrast by injecting a small quantity of the drug solution from the ampule intracutaneously in 240 cases. The results of this test, however, were not too good. Thirty per cent of the patients who had systemic reactions did not have positive reactions to skin tests, and, on the other hand, only 24 per cent of those who had positive reactions to skin tests had systemic reactions.

Reactions to sulfonamide compounds are always important. The incidence is not great, but when reactions do occur they are apt to be so severe that the possibility of producing them should not be overlooked. Raffetto and Nichols<sup>102</sup> gave sulfadiazine to a 10 year old girl in a course of treatment lasting for eight days. The child improved, and for four days use of the drug was omitted. Later, however, it was given again, and within two days a violent reaction involving the skin, the eyes, and the throat took place and the child almost died. The eosinophil count of the blood rose to 23 per cent. The time relationships should be noted.

99 Rackemann, F. M. Allergy. A Review of the Literature of 1942, *Arch Int Med* **71** 107 (Jan) 1943.

100 Archer, V. W., and Harris, I. D. An Ocular Test for Sensitivity to Diodrast Prior to Intravenous Urography, *Am J Roentgenol* **48** 763, 1942.

101 Robins, S. A. Hypersensitivity to Diodrast as Determined by Skin Tests, *Am J Roentgenol* **48** 766, 1942.

102 Raffetto, J. F., and Nichols, S. A. Nearly Fatal Reaction to Sulfadiazine in a Ten-Year-Old Girl Involving Skin, Eyes and Oropharynx, *J Pediat* **20** 753 1942.

in connection with Longcope's paper, to be discussed later. The interval of four days without treatment may or may not be important. The fact is that the reaction occurred fourteen days after the first dose had been given.

Hurd and Jacox<sup>103</sup> describe 2 cases of thrombopenic purpura which developed as a complication of treatment with sulfathiazole and sulfadiazine respectively. Both patients were old people in whom nosebleeds and purpuric spots developed, whose blood cells dropped from high to a low level and who needed multiple transfusions, in spite of which one of them died.

In *The Journal of the American Medical Association* are a series of case reports which are of considerable interest in connection with the use of sulfonamide drugs incorporated into ointments. Livingood and Pillsbury<sup>104</sup> in the Army used a 5 per cent sulfathiazole cream for various local infections of the skin in something over a thousand cases. In 12 cases reactions occurred, not at the time when the cream was applied but shortly afterward, when the drug was given by mouth for some new condition. Three of the 12 cases are described in detail. The sulfathiazole cream had been applied for approximately two weeks, and then after an interval, which was five days in 1 case, twelve days in another and fifty-eight days in the third case, sulfathiazole was given by mouth. Within three to eight hours each of the 3 patients had chills and fever with malaise and a generalized vesicular eruption. The authors recommend that local sulfathiazole therapy should not be used for more than five days at a time and that the indications for it should be considered carefully, if only because the local treatment is capable of producing a generalized sensitiveness which may jeopardize the patient's life if later he needs the drug for some serious general disease.

Cohen, Thomas and Kalisch<sup>105</sup> describe 2 patients with varicose eczema who were treated with sulfathiazole ointment and in whom fever and toxic rashes developed simply from the local absorption. They conclude that "sulfathiazole is potentially too dangerous to use indiscriminately in mild ailments."

103 Hurd, R. W., and Jacox, R. F. Thrombopenic Purpura Developing as a Complication of Sulfathiazole and Sulfadiazine Therapy, *J A M A* **122** 296 (May 29) 1943.

104 Livingood, C. S., and Pillsbury, D. M. Sulfathiazole in Eczematous Pyoderma, *J A M A* **121** 406 (Feb 6) 1943.

105 Cohen, M. H., Thomas, H. B., and Kalisch, A. C. Hypersensitivity Produced by the Topical Application of Sulfathiazole, *J A M A* **121** 408 (Feb 6) 1943.



Weiner<sup>106</sup> also had 4 patients who showed extreme local hypersensitivity to sulfathiazole. Each of them gave positive reactions to patch tests with the drug crystals, and in each the dermatitis cleared when the treatment was omitted.

Shaffer, Lentz and McGuire<sup>107</sup> exhibit excellent pictures of the generalized cutaneous lesions, some of them bullous, which may result from sensitization to sulfathiazole. They point out that the condition may be induced by the local application and be elicited later by oral exhibition. In a report of the Council on Pharmacy and Chemistry, Cole<sup>108</sup> declares that "Despite its value in some cases, the evidence of usefulness of sulfonamide compounds in dermatology is insufficient to justify their inclusion in New and Nonofficial Remedies." As he said "The sulfonamides act well in powder form, but should not be used until other measures fail. They should not be used for more than five days at a time, and their use should be limited to those cases in which the drug is prescribed by the doctor himself."

Weiner<sup>109</sup> draws further attention to the importance of eruptions due to sulfathiazole. He repeats that sensitization may develop from local application or from ingestion of the drug. When the drug is given again, the eruptions may be of the contact type, in which patch tests elicit positive reactions, or of the generalized disseminated variety, in which reactions to skin tests of the immediate type and/or passive transfer antibodies (reagins) may be occasionally demonstrated in the patient's serum. In sensitization to sulfonamide compounds the two types of allergy, local and general, can exist either singly or together.

The whole subject of reactions to drugs, particularly to the sulfonamide compounds, has been reviewed in a clear, masterly paper by Longcope<sup>110</sup>. A good many of the responses

can be compared easily to the reaction to foreign serum called "serum sickness." Longcope points out that different antigens vary in their ability to produce serum sickness and that the antigenic property can be increased by the addition of antibodies (immune serum is more likely to cause trouble than is normal serum) as well as by the admixture of bacterial filtrates and other products. It can be diminished somewhat by purification of the serum. "Despeciation" by treatment of the serum by heat, by acid or by alkali is sometimes helpful but may reduce the antibody content at the same time. Specificity is determined always by the chemical constitution, as Landsteiner has demonstrated. Reactions to drugs are often comparable to serum sickness. "Nirvanol," for example, is a sodium salt of phenylethylhydantoin. The drug is used in treatment of chorea, and it is not uncommon to have "nirvanol sickness" begin within six days after administration of the drug is started. It is as well defined as measles. Curiously, however, a second course of the drug rarely causes an immediate reaction. Cutaneous sensitivity cannot be demonstrated, no antibodies are found. Milian's erythema of the ninth day is a rash which may appear on the ninth or tenth day after a dose of neoparsphenamine. It also is analogous to serum sickness, and subsequent treatment may lead to serious reaction. As Dr. Longcope says, prevention of these disturbing symptom complexes consists, first, in thinking of the possibility, second, in asking the patient about his previous experiences with that substance, and, third, in making sure that the treatment is indicated and necessary. Reactions to eye tests and skin tests are interesting, but if the intravenous injection is given slowly and carefully, with an eye to the first signs of reaction, serious trouble will be avoided. Once the reaction of "serum sickness" has developed, there is no treatment which is really successful. Epinephrine is the best immediate symptomatic remedy.

*Atopic Eczema*—Eczema of the atopic type, so called neurodermatitis, may be due in part at least to a dietary deficiency. Burr<sup>111</sup> observed that when rats were fed on a diet from which all fat was excluded the skin became scaly, with necrosis of the tail, growth was retarded, lesions developed in the kidneys and the animals died. The feeding of fatty acids relieved the condition at once, and the fatty acids were more effective as they were more unsaturated. As might be expected, the skin did not clear unless growth and nutri-

106 Weiner, A. L. Cutaneous Hypersensitivity to Topical Application of Sulfathiazole, *J. A. M. A.* **121** 411 (Feb. 6) 1943.

107 Shaffer, B., Lentz, J. W., and McGuire, J. A. Sulfathiazole Eruptions. Sensitivity Induced by Local Therapy and Elicited by Oral Medication. Report of Four Cases with Some Allergic Studies, *J. A. M. A.* **123** 17 (Sept. 4) 1943.

108 Cole, H. N. The Local Use of Sulfonamide Compounds in Dermatology, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **123** 411 (Oct. 16) 1943.

109 Weiner, A. L. Cutaneous Eruptions Following Topical and Oral Sulfathiazole, correspondence, *J. A. M. A.* **123** 436 (Oct. 16) 1943.

110 Longcope, W. T. Serum Sickness and Analogous Reactions from Certain Drugs, Particularly the Sulfonamides, *Medicine* **22** 251, 1943.

111 Burr, G. D. Significance of the Essential Fatty Acids, *Federation* **1** 224, 1942.

tion were improved at the same time. In his paper is the picture of an infant with severe facial eczema. He was given 3 teaspoons of lard each day for a month, and the next picture shows his skin clear. The relations between various fatty acids, their sparing action one on the other and their relation to other vitamins are discussed. Di Sant'Agnese and Larkin<sup>112</sup> studied the capacity for absorption of vitamin A in 4 infants with eczema and found it greatly impaired. Deficiency may depend on faulty absorption as well as on inadequate feeding. Harris and Gay<sup>113</sup> treated 20 patients with infantile eczema with large doses of vitamin B (whole complex), but only 2 patients were healed, although 11 others were improved. Engman and MacCardle<sup>114</sup> found a new approach to the problem. They fed white rats on a magnesium-deficient diet and report that cutaneous lesions similar to those of neurodermatitis developed.

The relation between these deficiencies and the capacity to acquire sensitiveness must be considered, if only because there are so many cases in which a simple food allergy, to eggs or to cows' milk for example, appears to be an adequate cause for the disease. Skin tests elicit positive reactions, the food is eliminated, the child recovers. Whether this sensitization is conditioned by the total dietary and its proper absorption is a good question. Frei<sup>115</sup> studied the effect of variations in the vitamin A (carotene) intake and the development of hypersensitiveness to arsphenamine in guinea pigs, but he could find no variation in the degree of reactions before and after the treatment. This, however, was an "acute" experiment. McKhann, Spector and Meserve<sup>116</sup> in an excellent review on the celiac syndrome say that it is not clear whether the allergy is secondary to the gastrointestinal symptoms or vice versa. It is their impression that the difficulty with the absorption of fat is a result of the allergy and not a cause of it. Fries

and Mogil<sup>117</sup> took roentgenograms of children with the symptoms of gastrointestinal allergy. Gastric retention was the most common finding, but increased intestinal segmentation and colonic spasm were also observed. They say that these effects were not due to the nutritive composition of the food, but then they admit that flavorings in even small amounts may produce changes. Wing and co-workers<sup>118</sup> studied food allergy with the roentgen rays both in man and in the guinea pig. In the cases of 3 of 9 patients they felt sure that the abnormalities observed were not due to the nutritive factors but obviously the method is hard to control. This subject of infantile eczema and of neurodermatitis is important. There is neither time nor space to discuss it further here, but it is good to have several new suggestions as leads for further study.

#### MENIÈRE'S DISEASE AND MIGRAINE

Atkinson<sup>119</sup> has written a helpful paper on the relation between Ménière's disease and migraine. The auditory artery and the posterior cerebral artery are both branches of the basilar artery. It is easy to see how the vertigo of Ménière's disease and the scotoma of migraine can have a similar mechanism and be related. As said before, in the paragraphs on the chemical effectors, Atkinson distinguished between persons who have headaches of the vasodilator type ("red headaches"), a small group, with symptoms sometimes precipitated by allergy, sensitive to histamine and relieved by treatment with histamine, and persons with headaches of the vasoconstrictor type ("white headaches"), a much larger group, with no allergy, not sensitive to histamine and relieved by nicotinic acid. Combinations of headaches and dizziness are common, and one finds "migraine with vertigo" or "Ménière's syndrome with headache." The frequency is shown in a tabulation adapted from Atkinson's paper.

#### Ménière's Disease

	Vasodilator Group	Vasoconstrictor Group
With migraine	10	12
With nonspecific headache	6	36
No headache	4	40
Total	20	88

117 Fries, J. H., and Mogil, M. Roentgen Observations on Children with Gastrointestinal Allergy to Foods, *J. Allergy* **14** 310, 1943.

118 Wing, W. M., Smith, C., Borne, W. H., and Cooke, R. A. Spontaneous and Induced Sensitivity to Food Stuffs. X-Ray Studies of the Small Intestine in Man and Guinea Pig, *J. Allergy* **14** 56, 1942.

119 Atkinson, M. Ménière's Syndrome and Migraine. Observations on a Common Causal Relationship, *Ann. Int. Med.* **18** 797, 1943.

112 di Sant'Agnese, P. A., and Larkin, V. deP. Vitamin A Absorption in Infantile Eczema, *Proc. Soc. Exper. Biol. & Med.* **52** 343, 1943.

113 Harris, A., and Gay, L. N. The Use of Vitamin B Complex in the Treatment of Infantile Eczema, *J. Allergy* **14** 182, 1943.

114 Engman, M. F., Jr., and MacCardle, R. C. A New Approach to the Problem of a Disseminated Neurodermatitis, *Arch. Dermat. & Syph.* **46** 337 (Sept.) 1943.

115 Frei, W. Further Studies in Arsphenamine Hypersensitiveness in Guinea Pigs. IV. Vitamin A (Carotene) in Relation to the Sensitization of Guinea Pigs to Old Arsphenamine, *J. Invest. Dermat.* **5** 117, 1942.

116 McKhann, C. F., Spector, S., and Meserve, E. R. An Association of Gastro-Intestinal Allergy with the Celiac Syndrome, *J. Pediat.* **22** 362, 1943.

The history is helpful, for in the vasodilator group the headache comes first, before the dizziness, which often "explodes" in a sudden attack, while in the vasoconstrictor group the vertigo comes first, with headache later. Meantime, Trowbridge and co-workers<sup>120</sup> find that the conventional methods of symptomatic treatment of migraine are effective so far as the one attack is concerned. Ergotamine tartrate gave complete relief in 80 per cent of the cases in which it was used. Morphine was effective in 59 per cent, phenobarbital in 16 per cent and acetylsalicylic acid in 10 per cent.

#### INSULIN ALLERGY

Insulin allergy may be a troublesome complication. Goldner and Ricketts<sup>121</sup> found that 20 per cent of patients treated with insulin manifest mild local reactions after the first week of treatment, which, however, disappear as the treatment continues. In 8 cases the sensitiveness persisted or developed at a later time. This was especially the case when the patient had neglected to take insulin regularly and when the time interval was sufficient to allow the sensitizing effect of the early treatment to develop. The lapse in therapy was important. Prevention of further local reaction was effected by injecting insulin in small increasing doses at intervals of only a few hours. Watson<sup>122</sup> found insulin allergy in 5 per cent of his insulin-treated diabetic patients. Weitz<sup>123</sup> describes a patient whom he had desensitized successfully and adds that the positive reactions to skin tests and the antibodies (reagins) to insulin which were present at the start disappeared later. Lowell<sup>124</sup> has found two antibodies for crystalline insulin. One is concerned with the allergy and, like other reagins, is destroyed by heating the serum at 56 C for an hour; the other is concerned with resistance to insulin. A patient who gave a positive reaction to a skin test with insulin showed no reduction of the blood sugar level when crystalline insulin was injected. Her tolerance to crystalline insulin was abnormally high. Her serum protected mice against lethal doses of crystalline insulin. Toward

human insulin she behaved differently. The skin test elicited a positive reaction as before, but the blood sugar level dropped when human insulin was given. Her tolerance for human insulin was normal. Her serum was not effective in protecting mice against human insulin. The reason for the discrepancy is hard to explain.

#### ALLERGY TO INJECTABLE LIVER EXTRACTS

Fernberg, Howard and Young<sup>125</sup> add 8 cases to the list of 29 reviewed in 1940 by Harten and Walzer<sup>126</sup>. They made skin tests on their patients with ten different commercial preparations of liver; they also applied fresh juices from beef, hog, horse and human livers and extracts of other organs. All their patients reacted to the purified liver extracts but not to the proteins of muscle, kidney or stomach except for slight responses in 1 or 2 instances. The authors conclude that the allergy is directed to the anti-anemic factor in the liver and that this is a potent allergen which contains neither protein nor carbohydrate and which is not species specific or organ specific. I quote "Attention is called to the potential immunologic significance of the demonstration of an antigen residing in a fraction of an organ tissue."

#### INSECT BITES

There are three reports dealing with severe reactions to insect bites. From Kenya Colony comes the report of Jex-Blake<sup>127</sup> that a patient was stung by bees twelve times during twenty years with no ill effects. Then, after another bee sting he became acutely ill, pulseless, cyanotic and unconscious for about ten minutes. Nine months later he was bitten again, and this time he died within fifteen minutes. Similar is the case reported by Helm<sup>128</sup>.

Mease<sup>129</sup> describes a man working in a Florida orange grove, where he was miserable because of severe reaction to the bites of deer flies. Thirty flies were collected and macerated in 30 cc of buffered saline solution, and skin tests with the filtered extract were made on the patient as well as on normal persons. The normal persons gave

120 Trowbridge, L. S., von Storch, T. J. C., and Moore, M. The Drug Therapy of Migraine Headache, *New England J. Med.* **227** 699, 1942.

121 Goldner, M. G., and Ricketts, H. T. Insulin Allergy. A Report of Eight Cases with Generalized Symptoms, *J. Clin. Endocrinol.* **2** 595, 1942.

122 Watson, E. M. Nonhypoglycemic (Allergic) Insulin Reactions, *Canad. M. A. J.* **47** 336, 1942.

123 Weitz, M. A. Insulin Hypersensitivity with Desensitization, *J. Allergy* **14** 220, 1943.

124 Lowell, F. C. Evidence for the Existence of Two Antibodies for Crystalline Insulin, *Proc. Soc. Exper. Biol. & Med.* **50** 167, 1942.

125 Fernberg, S. M., Howard, L. A., and Young, R. H. Allergy to Injectable Liver Extracts. Clinical and Immunological Observations, *Ann. Int. Med.* **18** 311, 1943.

126 Harten, M., and Walzer, M. Annual Review Allergy to Insulin, Liver, Pituitary, Pancreas, Estrogens, Enzymes, and Similar Substances, *J. Allergy* **12** 72, 1940.

127 Jex-Blake, A. J. Bee Stings in Kenya Colony, *Brit. M. J.* **2** 241, 1942.

128 Helm, S. Severe Anaphylactic Reaction to Bee or Wasp Sting, *Mil. Surgeon* **92** 64, 1943.

129 Mease, J. A. Deer Fly Desensitization, *J. A. M. A.* **122** 227 (May 22) 1943.

no reaction, but the patient gave an immediate urticarial wheal response. In view of this, desensitization was carried out. The man was treated with doses of the extract given subcutaneously on the second, fourth, seventh and eleventh days and thereafter for ten weekly intervals. Meantime, the flies no longer bothered him. The next spring he was given more injections, and since then for four years he has been "cured."

Longcope<sup>110</sup> compares reactions to drugs to serum disease. It is easy to compare other and even more dramatic episodes to anaphylaxis itself. In these there are three factors: first, the original treatment, which may be likened to the sensitizing dose; second, a period of time without treatment, the incubation period; and, third, the subsequent dose, which is followed often and promptly by a severe and literally shocking reaction. This sequence occurs in some of the cases of reaction to drugs. Sulfonamide drugs are given for gonorrhea at the age of 26 and no trouble results, but when such compounds are

given again to the same man for pneumonia or meningitis at the age of 32 severe symptoms develop at once. This occurs with insulin and with liver preparations and with insect bites. Is it possible that other allergies, like hay fever or hypersensitivities to dogs or cats, are aggravated by the fact that exposure is intermittent, sometimes with years between the periods of contact?

As for our boys overseas, thank God that each and every one of them has been immunized actively with diphtheria and tetanus toxoids and with gas bacillus vaccine and that many have been immunized with the yellow fever virus. Foreign serum is no longer to be reckoned with except in odd cases. Reactions to human plasma are reported and will be reviewed later when more is known about them. This is no time to cast any aspersions on a method which has saved so many lives but one can hope that the study of these reactions which is going on all over the world will lead to still greater advances in knowledge.

263 Beacon Street

**Gastro-enterology** By Henry L. Bockus, M.D.  
Volume I Price, \$12 Pp 831 Philadelphia W B  
Saunders Co, 1943

The first volume of what promises to be a monumental work on gastroenterology discusses the esophagus and the stomach. Volume II is to deal with the small and large intestines and the peritoneum, and volume III, with the liver, the biliary tract and the pancreas.

The book makes its beginning, in section I, with five chapters on the examination of the patient. The first chapter has to do with history taking, and in view of the detailed discussion of diseases of the stomach and the esophagus elsewhere it would seem that the ten pages devoted to history taking is rather brief. In this section the other chapters have to do with symptomatology, with the physical examination and with the laboratory examinations.

Section II has to do with the esophagus and the diaphragm. Eleven chapters are devoted to applied anatomy and physiology of the esophagus, stricture, cardiospasm, tumors, esophageal hiatus hernia and so on.

Section III, on disorders of the stomach, makes up the bulk of the volume, 624 pages. It is readily appreciated, therefore, that the subject is covered with minute attention to every phase. The introductory chapters have to do with the applied anatomy and physiology of the stomach, but the remainder of the section is devoted to the pathology, the diagnosis and the treatment of various gastric diseases.

Only the most favorable comments can be made about this tremendous undertaking of Dr. Bockus. The book is the product of an ingenious, fertile and retentive mind. One of the agreeable features of the book is that Bockus uses the first person singular repeatedly and expresses his own definite opinions about nearly everything he discusses. Most readers appreciate the personal touch in their reading. One minor criticism is that Bockus is not quite sure when a patient is a patient or a case. As a rule one treats a patient rather than a case, the patient dies and not the case.

The format in every way is excellent. The paper is glossy and permits of excellent reproduction of roentgenograms, drawings and photographs. Some of the photographs, incidentally, are colored. This first volume is well indexed, and there are innumerable references. The book can be recommended not only for its excellent appearance but, what is much more important, for its intelligent and thoughtful presentation. It should appeal to the internist irrespective of whether or not he classifies himself as a gastroenterologist. It should be on his bookshelf. Surgeons and other specialists who may have occasional problems dealing with the gastrointestinal tract would probably consult it frequently in a medical library in order to have an authoritative and last word observation on a subject in which they are probably only remotely interested.

**Pathology and Therapy of Rheumatic Fever** By Leopold Lichtwitz, M.D. Foreword by William J. Maloney, M.D., LL.D., F.R.S. (Edin). Edited by Major William Chester, M.C., A.U.S. Price, \$4.75 Pp 211 New York Grune and Stratton, 1944

For many years rheumatic fever has been the subject of profound and tireless investigation by eminent clini-

cians, bacteriologists, pathologists, public health workers and other investigators. While much progress has been achieved toward a better understanding of the disease, it is generally conceded that the causation of rheumatic fever is still unsettled but that several factors participate. It is therefore amazing to note the uncompromising views expressed by the author of this text. The opening sentence of the book clearly depicts this: "Rheumatic fever is a noninfectious disease." The author contends that rheumatic fever is caused, not by a specific micro-organism or virus, but by a sensitization to antigens, protein in nature, which in most cases are products of micro-organisms. All consequent arguments are based on this premise.

The conventional ideas of incidence and personal factors of rheumatic fever are considered. The pathologic changes of the disease as they occur in various parts of the body are discussed in considerable detail. The author states that Aschoff bodies are neither specific to rheumatic fever nor pathognomonic of it and briefly dismisses the controversial issue regarding what he calls analogous lesions. He writes that such lesions occur in other infectious diseases. In the last paragraph on page 42 is found the following remarkable statement: "The collagen fibrils swell, and the auricular endothelium, losing its epithelium, undergoes necrosis." It is possible that the word epithelium is a typographic error.

All possible forms of therapy are discussed in detail. Tonsillectomy is condemned, but the local treatment of infected tonsils, a method long since frowned on by leading otolaryngologists, is advocated. While tonsillectomy neither cures nor prevents rheumatic fever, definite indications for its performance frequently occur.

The reviewer is fully aware of the uncertainties that prevail today regarding the causation of rheumatic fever and therefore cannot subscribe to the unequivocal views expressed in this book. The allergic factor in rheumatic fever is generally accepted, but with the evidence at hand it cannot be looked on as the sole cause. The book contains numerous inconsistencies and contradictions.

**The Role of Nutritional Deficiency in Nervous and Mental Disease** Research Publications, Association for Research in Nervous and Mental Disease. Volume XXII. Price, \$4 Pp 215 Baltimore Williams & Wilkins Company, 1943

This excellent book of two hundred pages consists of the proceedings of the December 1941 meeting of the Association for Research in Nervous and Mental Disease. It is a symposium on the role of nutritional deficiency in neuropsychiatric disorders and includes sixteen articles, each of which was contributed by an expert in his particular field of endeavor. The first half of the volume is devoted to papers which summarize contributions from the fundamental sciences, the second, to reports on clinical aspects of the subject. The opening chapters are of general interest, the first containing a brief discussion of outstanding facts gleaned from physiologic investigations of animal nutrition and the second dealing with the relation of enzymes to deficiency disease. Subsequent articles are devoted to the role of vitamins in brain metabolism, general problems of nutritional deficiency, the thiamine content of human tissue,

the pathology of deficiencies of the vitamin B group, vitamin A and the nervous system and vitamin E deprivation. The second part of the book includes discussions of the clinical aspects of human thiamine deficiency, experimentally induced, mental and neurologic aspects of vitamin B complex deficiencies, emotional disturbances in pellagra, multiple neuritis, phenylpyruvic oligophrenia, pernicious anemia and allied disorders, the psychoses and nutritional deficiency, and the prevention and cure of nutritive failure.

Appended to each article is the discussion which followed presentation of the paper. This is exceedingly valuable in clarifying, and often resolving, apparently inconsistent findings and in presenting the rationale of divergent opinions on a number of controversial subjects.

The book is highly recommended, not only to the neuropsychiatrist but to all clinicians interested in the general problems of deficiency disease.

#### Office Treatment of the Nose, Throat and Ear

By A. R. Hollender, M.D., Associate Professor of Laryngology, Rhinology and Otolaryngology, University of Illinois College of Medicine. Price, \$5. Pp. 480, with 120 illustrations. Chicago: Year Book Publishers, Inc., 1943.

This is an attractive book which physicians and medical students will be glad to know. The author says that a large number of diseases of the nose, throat and ear should be treated at the office rather than in the hospital, and he proceeds to describe each of these and how they should be managed.

He has divided his subject-matter into two parts. The first gives a general survey of the field and an account of the available therapeutic measures, the second describes techniques to be utilized. The whole makes up an excellent handbook, practical as can be.

The illustrations in the technical section are unusually good, so that one can readily see how the different tools that the modern otolaryngologist has at his command should be manipulated. The writing throughout is simple and unaffected, and the author's meaning is always understandable. At the end of each of the twenty-three chapters is a short bibliography selected critically to develop further information around the topics discussed.

The methods of treatment which are advocated often seem relatively simple, are described in detail and appear to be based on a solid foundation of common sense and experience. On the whole, here is a book that a great many physicians will find useful, and students or interns will swear by it.

#### A Textbook of Medicine

By American Authors. Edited by Russell L. Cecil, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College. Associate Editor for Diseases of the Nervous System, Foster Kennedy, M.D., F.R.S.E., Professor of Clinical Neurology, Cornell University Medical College. Sixth Edition, Revised and Entirely Reset. Price, \$9.50. Pp. 1,566, with 195 illustrations and charts. Philadelphia: W. B. Saunders Company, 1943.

One hundred and fifty-four authors have collaborated under the editorship of Drs. Cecil and Kennedy to produce this book. It is the sixth edition of this well known textbook, which first appeared in 1927. Any work that goes through six editions in fifteen years may be accepted as worth while. The book is familiar

to most physicians, but the present edition contains much that is new and much that has been thoroughly rewritten. Aviation medicine, air sickness, virus pneumonia and hirudinea represent a few of the innovations. The form of the book has been changed so that much new material has been added without increasing the already large size too much. As a matter of fact, there are fewer pages, but the larger page size and the arrangement of the material in double columns more than make up for that.

This work still remains a standard one for students, teachers and practitioners.

#### Modificacoes de forma do eletrocardiograma

By Dante Pazzanese. Pp. 373. São Paulo, Brazil: Grafica da Prefeitura, 1942.

The author emphasizes the importance of employing a proper technique when recording an electrocardiogram. He presents tracings showing patterns characteristic of infarction that are due to technical errors. Several such types of tracings are presented throughout the monograph to emphasize the importance of controlling technique, variations in the patient's habitus and certain normal physiologic phenomena when interpreting electrocardiograms. Some of the records are interesting.

There are many illustrations. Most of them are clear, but too many are poor. The author approaches the problem in more or less the same fashion as followed in other monographs. He does not employ any new or truly original lines of presentation. As in most monographs on the subject, there is no simplification of the subject. The book fails to fulfil the needs of a beginner who is interested in electrocardiography for the first time. There is little of interest to one who is already trained in the subject, to him the volume is just another book on electrocardiography. It does, however, fulfil a need in that it makes a monograph on the subject available to physicians who are better acquainted with the Portuguese language than with English.

#### Pain

By thirty-seven contributors. Research Publications of the Association for Research in Nervous and Mental Disease. Volume XXIII. Price, \$7.50. Pp. 468. Baltimore: Williams & Wilkins Company, 1943.

This volume maintains the high standards set by the previous research publications. In 1942 the subject of pain was selected as the topic for the annual meeting of the organization. Thirty-seven different contributors, with associates in some instances, have made possible a 468 page discussion of what is, to make a trite statement, the most important symptom subjectively in the category of symptoms, namely pain. This "simple sensory experience" is discussed from innumerable points of view. The symposium starts out with a physiologic and psychologic discussion of pain and continues more specifically in the field of special types of pain, such as those that occur in heart disease, in headache and in diseases of the digestive tract and of other important organs and systems of the body. Altogether the subject of pain is treated in a comprehensive fashion, and the reader of this publication will obtain a broad knowledge of what pain is, how pain expresses itself, what can be done for painful conditions, how important pain is in diagnosis and so on ad infinitum. The reviewer considers this book to be an important contribution and recommends it most highly.



**Internal Medicine in General Practice** By Lieutenant Robert Pratt McCombs (MC) U S N R, recently Instructor in Internal Medicine for the State-wide Postgraduate Program of the Tennessee State Medical Association Price, cloth, \$7 Pp 694, with 114 illustrations and figures Philadelphia W B Saunders Company, 1943

This is a textbook of medicine that begins at a little higher level than the textbook for students. It attempts to do what the title indicates, namely, to present a post-graduate course in medicine for general practitioners. It does this reasonably well. It covers a surprisingly wide range of subjects in a rather abbreviated fashion and points out the salient diagnostic features of and the therapeutic pitfalls that lie in various diseases. It reviews the detail of history taking and of physical diagnosis and is well up-to-date on its coverage of new disease entities and new therapeutic agents. The book will be of considerable value to the busy wartime general practitioner, and it is pointed out in the foreword that it may serve a purpose among physicians in the armed services when they are called on to meet situations with which they are not entirely familiar.

**The Compleat Pediatrician** By Wilbur C Davison, M D, Professor of Pediatrics, Duke University School of Medicine Price, \$3.75 Durham, N C Duke University Press, 1943

The "Compleat Pediatrician" fills the same admirable purpose in this edition that it has in three earlier ones, it has no peer as a "bedside guidebook" for student and practitioner alike.

Many revisions have been made, all eminently practical and all designed to serve as stimulating reminders of a broader coverage of medical knowledge contained in larger, more conventional textbooks.

Only by a brief study of the volume can one appreciate its great usefulness, the division of subjects follows a logical order, and any one using the volume for the purpose intended will find it an invaluable aid. Brief descriptions and evaluations of newer laboratory procedures should be most helpful to busy practitioners.

This book should be on the desk or in the kit of any physician who deals with infants and children.

**Elements of Medical Mycology** By Jacob Hyams Swartz Price, \$4.50 Pp 190, with 80 illustrations and 1 chart New York Grune and Stratton, Inc, 1943

The best part of this little manual is the systematic descriptions and illustrations of the various fungi. The clinical descriptions are too brief to be of a great deal of value, and here and there are statements with which the reviewer does not entirely agree. It is his impression, for example, that precipitation and complement fixation tests for coccidioidomycosis are now well established as diagnostic procedures. The book is finely printed and beautifully illustrated, there are bibliographies and an index, and on the whole it should prove useful as an introduction to the subject.

**Applied Dietetics** By Frances Stern Second edition Price, \$4 Pp 267, with 57 tables Baltimore Williams & Wilkins Company, 1944

Miss Stern stands out as a pioneer figure in modern dietetics, the preface of her book recalls that the food clinic at the Boston Dispensary was opened as long ago as 1918. It must be a source of gratification to the author, who worked so hard and for so many

years to encourage others, to see the food clinic now universally recognized as an integral part of any outpatient department. Miss Stern's book contains the usual machinery of such compendiums—diet lists, tables of food values, etc. Special emphasis is on the normal diet and the environmental factors which influence it. Above all the education of the patient is stressed. It is a pleasure to welcome after nine years the appearance of a new edition of this useful book.

**Clinical Lectures on the Gallbladder and Bile Ducts** By Samuel Weiss Price, \$5.50 Pp 504, with 125 figures and 21 tables Chicago Year Book Publishers, Inc, 1944

The method of dealing with a subject in a series of lectures takes one back to the nineteenth century, when it had a high degree of popularity. One may believe that the writer by assembling a series of lectures implies a somewhat informal discussion and perhaps relieves himself from the responsibility of systematically covering all aspects of a subject. Lectures may also be assumed to reflect a highly personal point of view. The present volume, however, covers the subjects of the gallbladder and the bile ducts thoroughly and adequately. The illustrations are profuse and well selected, and there are good bibliographies.

**Handbook of Nutrition A Symposium** Prepared by Council on Foods and Nutrition of American Medical Association Price, \$2.50 Pp 586 Chicago American Medical Association, 1943

Most physicians have seen these excellent articles in *The Journal of the American Medical Association* as they have appeared during the past year or so. The subjects of nutrition in general, vitamins, vitamin deficiency and minerals in nutrition are thoroughly covered by outstanding authorities. The volume furnishes a mine of information as well as a thorough bibliography of the recent literature.

**Medical Physics** Editor in Chief, Otto Glasser. Price, \$18 Pp 1744, with numerous figures and tables Chicago The Year Book Publishers, Inc, 1944

This monumental compendium of 1,744 pages (folio) dealing with the application of physics in medicine is really a small encyclopedia. Alphabetically arranged there are hundreds of brief articles dealing with all sorts of subjects. Thus if one opens at random one comes across "Massage," "Mathematical Biophysics," "Matter Structure," "Metabolism Apparatus" and "Methods." A series of articles on "Roentgenography" runs from page 1262 to 1330, to be followed by 70 pages on "Roentgen Rays." Then comes "Shock," "Sound," etc. The articles are concise, written by well known authorities and plentifully illustrated with photographs, charts and tables. There are adequate indexes, and the material is easy to find. One is impressed by the need of just this sort of reference book.

**Neurology** By Roy R Grinker, M D Third edition. Price, \$6.50 Pp 1075 Springfield, Ill Charles C Thomas, Publisher, 1943

As a comprehensive textbook in one volume, this edition of "Neurology" is to be recommended above any other text. Previous editions are well known for the successful inclusion of fundamental anatomic and physiologic knowledge in a clinical book. This edition has followed the same policy but has improved on the



clinical discussions and has omitted none of the significant neurologic conditions. The latest in diagnostic and therapeutic technics are presented in good detail and are too numerous to be listed here. The book carries authority because of the writer's own studies on a wide range of neurologic problems.

This volume is well proportioned and intelligently written, it is therefore pleasant reading. It is a large book but is \$2 cheaper than previous editions.

**Primeras reuniones extraordinarias de la Asociacion de medicos del Hospital Durand.** Edited by Dr. Jose Alberto Pique. Pp. 675 and 1428 (two volumes). Buenos Aires, Argentina, 1942.

These two volumes contain papers presented by the members of the staff of the Durand Hospital at the staff meetings held intermittently throughout the year. The selection of subjects is catholic, they extend from occupational diseases and glaucoma to therapeutic abortion and acute appendicitis. The articles might be welcomed by general practitioners, though the treatment of some of the subjects is probably far beyond their fundamental knowledge. The subjects in which specialists might be interested are few and far between. The book consequently is neither fish, fowl nor good red herring and would have a limited appeal to American physicians.

It does show concretely, however, that a hospital staff can have excellent meetings and that they can be carried through in more than a perfunctory manner.

**Family Nutrition.** Published by the Philadelphia Child Health Society. Price, 50 cents. Pp. 119, with 22 tables, 10 charts and 26 illustrations. Philadelphia, 1943.

This brochure gives an admirable summary of the problems of nutrition. The usual facts about calories, vitamins, etc., are well stated, but in addition there is much useful material on the nutritional status of groups, diet in relation to public health problems and menu planning for various groups. The material is well organized, with excellent diagrams and charts.

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#### CORRECTION

In the article by Captain John E. Leach entitled "Effect of Roentgen Therapy on the Heart: A Clinical Study," which appeared in the December 1943 issue (*ARCH. INT. MED.* 72:715, 1943), the word "arrhythmia" is spelled incorrectly, without the "h."

## DERMATOMYOSITIS

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Dermatomyositis is frequently unrecognized because of lack of familiarity with its variable clinical manifestations. In the advanced stage of the illness the diagnosis is seldom difficult. This report concerns the clinical and laboratory findings and biopsy observations on muscle in the cases of 9 patients with dermatomyositis who were observed in Vanderbilt Hospital during one year. A certain number of the cases in this series were atypical, yet there were sufficient significant features to justify this diagnosis.

The cause of dermatomyositis is unknown. Frequently the earliest symptom is preceded by an acute infection. Although this disease may occur at any age, it usually occurs between the ages of 10 and 50 years. There is no significant sex predominance. Pathologically the salient lesions are present in the striated muscles, however, many other structures may be implicated. The onset of the disease may be abrupt or insidious, remissions and exacerbations are frequent. The course of the illness varies from weeks to years. The outcome is reported to be fatal in 50 to 60 per cent of the cases.

The most characteristic feature of this disease is the involvement of muscles, which often produces the earliest symptoms. Muscular pains, tenderness, stiffness and fatigue are common complaints and may be localized or generalized at the onset of the illness. As the disease progresses, the muscles of the shoulder and of the pelvic girdle as well as the proximal muscles of the extremities are affected in particular. The consistence of the involved muscles is variable. Late in the illness atrophy and contractures of the muscles may occur. The extrinsic orbital muscles, the muscles of the jaw, tongue, pharynx and larynx, the intercostal muscles and the diaphragm may be affected. Involvement of the diaphragms with subsequent respiratory paralysis or pulmonary infection is the most common cause of death. There is both clinical and anatomic evidence to show that the heart may be

involved, although this is not common.<sup>1</sup> Rarely death may result from cardiac failure.

Cutaneous lesions usually develop during the illness. While ordinarily erythematous, the eruption is nonspecific and may simulate a variety of dermatologic conditions.<sup>2</sup> Other cutaneous manifestations include hyperhidrosis, loss of hair, pigmentation, telangiectases, sclerodermatous changes and subcutaneous calcification. There may be lesions of the mucous membranes.<sup>3</sup> Brawny or soft edema, often accompanied by erythema, is a frequent finding. Vasomotor disturbances, particularly Raynaud phenomena, are present in many instances and may constitute the earliest symptoms.

Headache, fever, easy fatigability and loss of weight are common complaints. There may be paresthesias or muscular cramps. Hemorrhagic manifestations, with purpura, epistaxes and bleeding into the intestine and kidneys, have been observed.<sup>4</sup> There may be arthritic pains, although these usually have been ascribed to

1 (a) O'Leary, P. A., and Waisman, M. Dermatomyositis. A Study of Forty Cases, *Arch Dermat & Syph* **41** 1001-1019 (June) 1940. (b) Schuermann, H. Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), *Arch f Dermat u Syph* **178** 414-468, 1939. (c) Kinney, T. D., and Maher, M. M. Dermatomyositis. A Study of Five Cases, *Am J Path* **16** 561-594 (Sept) 1940. (d) Keil, H. Dermatomyositis and Systemic Lupus Erythematosus. II. A Comparative Study of the Essential Clinicopathologic Features, *Arch Int Med* **66** 339-383 (Aug) 1940.

2 (a) Keller, R. Zur Dermatomyositis im Kindesalter, *Ztschr f Kinderh* **58** 551-563, 1936. (b) Karellitz, S., and Welt, S. K. Dermatomyositis, *Am J Dis Child* **43** 1134-1149 (May) 1932. (c) Keil, H. The Manifestations in the Skin and Mucous Membranes in Dermatomyositis with Special Reference to the Differential Diagnosis from Systemic Lupus Erythematosus, *Ann Int Med* **16** 828-871 (May) 1942.

3 O'Leary and Waisman.<sup>1a</sup> Schuermann.<sup>1b</sup> Keil.<sup>2c</sup>

4 (a) Schuermann.<sup>1b</sup> (b) Marcus, I. H., and Weinstein, J. Dermatomyositis. A Report of a Case with a Review of the Literature, *Ann Int Med* **9** 406-425 (Oct) 1935. (c) Keil, H. Dermatomyositis and Systemic Lupus Erythematosus. I. A Clinical Report of "Transitional" Cases with a Consideration of Lead as a Possible Etiologic Factor, *Arch Int Med* **66** 109-139 (July) 1940.

From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

tendinous and periarticular involvement rather than to actual disease of joints<sup>5</sup> Additional findings have included retinal changes,<sup>6</sup> splenomegaly and hepatomegaly, enlargement of lymph nodes,<sup>7</sup> effusions into body cavities<sup>1b</sup> and decreased tendon reflexes<sup>8</sup> The laboratory and pathologic aspects of this disease will be mentioned later

The diagnosis of dermatomyositis depends on clinical and pathologic observations In the differential diagnosis, most difficulty arises in distinguishing dermatomyositis from scleroderma Much clinical and pathologic evidence has been presented to show that these two conditions are merely variations of a single disorder<sup>9</sup> Certain observers, however, contend that they are clinically and pathologically distinct<sup>10</sup> Disseminated lupus erythematosus, periarteritis nodosa, early rheumatic fever, early rheumatoid arthritis, trichiniasis, polyneuritis and epidemic myalgia are only a few of the conditions which may be confused with dermatomyositis

Treatment of dermatomyositis has been unsatisfactory In many instances salicylates do not relieve the muscular symptoms<sup>11</sup> Milhorat and his co-workers<sup>12</sup> noted some clinical improvement after administration of vitamin E Other therapeutic measures have included rest, physical therapy, administration of potassium iodide, transfusions, administration of vitamins,

treatment with neoarsphenamine and inhalations of oxygen

#### REPORT OF CASES

CASE 1—H H, a 59 year old white farmer, was well until eight years prior to admission to the hospital, when there was a gradual onset of generalized weakness, stiffness and soreness of the muscles Soon afterward there appeared dyspnea on exertion, anorexia and slight dysphagia During the prolonged illness his weight fell from 220 to 120 pounds (99 to 54 Kg) Four years before admission the patient began to have recurrent attacks of symmetric discoloration and pain of the fingers, hands and lower part of the forearms after exposure to cold air One year later, after a severe attack of "influenza," a chronic productive cough developed In the four year period prior to admission to the hospital the patient was followed irregularly in the outpatient clinic, where it was felt that the majority of his complaints were psychogenic In March 1939 he was found to have a scaly papular

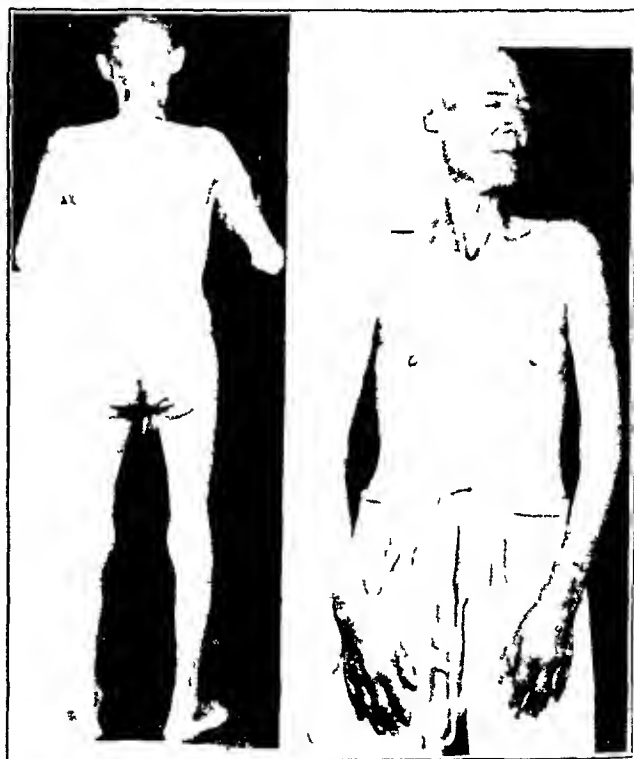


Fig 1 (case 1)—Muscular atrophy and areas of pigmentation over the spine are apparent

reddened eruption over the face, trunk and scrotum Because of progressive weakness and fatigue, the patient was admitted to the hospital on July 17, 1941 The past history and family history were not contributory

**Physical Examination**—This revealed an emaciated white man The skin of the face and of the distal portions of the extremities was thickened and adherent to underlying structures Over the lower part of the lumbar region of the spine and the gluteal region the skin was thickened and exhibited a bluish brown discoloration The scrotum showed splotchy brown pigmented areas Numerous telangiectases were present on the face Muscular atrophy, while generalized, was most striking in the sternomastoid muscles and the muscles of the shoulder and pelvic girdles The musculature of the proximal portions of the extremities was more atrophic than that of the distal portions The muscles were flabby and presented diffuse moderate tenderness The chest was emphysematous Moist rales

5 O'Leary and Waisman<sup>1a</sup> Keil<sup>1d</sup> Marcus and Weinstein<sup>4b</sup>

6 Bruce, G M Retinitis in Dermatomyositis, *Tr Am Ophth Soc* **36** 282-297, 1938 Schuermann<sup>1b</sup> Keil (footnotes 1d and 4c)

7 (a) Holler, G Ein Fall von isolierter Polymyositis, *Wien med Wchnschr* **89** 321-325 (March 25) 1939 (b) Keil<sup>1d</sup>

8 O'Leary and Weisman<sup>1a</sup> Marcus and Weinstein<sup>4b</sup>

9 (a) Freudenthal, W Generalized Scleroderma and Dermatomyositis A Histological Comparison, *Brit J Dermat* **52** 289-295 (Oct) 1940 (b) Lewis, T Notes on Scleroderma (Dermatomyositis), *ibid* **52** 233-242 (Aug-Sept) 1940 (c) Dowling, G B Generalized Scleroderma, *ibid* **52** 242-256 (Aug-Sept) 1940 (d) Hecht, M S Dermatomyositis in Childhood, *J Pediat* **17** 791-800 (Dec) 1940

10 Brock, W G Dermatomyositis and Diffuse Scleroderma Differential Diagnosis and Reports of Cases, *Arch Dermat & Syph* **30** 227-240 (Aug) 1934 Banks, B M Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? *New England J Med* **225** 433-444 (Sept 18) 1941 O'Leary and Waisman<sup>1a</sup> Keil<sup>1d</sup>

11 Schuermann<sup>1b</sup> Holler<sup>7a</sup>

12 Milhorat, A T, Weber, F C, and Toscani, V Metabolic Studies in Dermatomyositis with a Note on the Effect of Wheat Germ, *Proc Soc Exper Biol & Med* **43** 470-473 (March) 1940

were present at the base of each lung. The heart was within normal limits. The blood pressure was not elevated. The liver was slightly enlarged. There were cyanosis and early clubbing of the nail beds. Slight brawny pitting edema was present over the ankles.

**Laboratory Studies**—There was no anemia. The total leukocyte count was 10,600 per cubic millimeter, with a differential count of 71 per cent neutrophils, 6 per cent eosinophils, 17 per cent lymphocytes and 6 per cent monocytes. Examinations of the urine and stools showed them to be normal. The total serum protein amounted to 8 Gm per hundred cubic centimeters, with albumin 3.7 Gm and globulin 4.3 Gm. Roentgenograms of the sinuses, chest and long bones showed no abnormality. Fluoroscopic examination of the chest showed diminished excursion of the diaphragm and poor expansion of the thoracic cage. An electrocardiogram showed deviation of the axis to the right with a normal sinus rhythm. The basal metabolic rate was  $+3$  per cent.

**Biopsy**—A section of skin showed atrophy of the epidermis and slight perivascular lymphocytic infiltration of the corium. A biopsy of the gastrocnemius muscle showed a pronounced focal increase in the muscle nuclei, degenerating muscle fibers, some of which were undergoing phagocytosis, focal increase in interstitial tissue, moderate infiltration of inflammatory cells into the interstitial substance, occasional multinucleated cells, and focal collections of brown pigment granules in the interstitial connective tissue.

**Course in the Hospital**—The patient was observed for fifteen days. During this time the temperature and pulse remained normal. Therapy consisted of frequent warm baths and oral administration of potassium iodide, acetylsalicylic acid and 40 mg of alpha tocopherol daily. The vital capacity was slightly reduced. The venous pressure and the circulation time were normal. The patient was digitalized, without improvement. At the time of his discharge his condition was unchanged.

One month later he reentered the hospital for a period of six weeks. Because of anorexia, increased weakness and persistent abdominal fulness, he had remained in bed during the intervening period. On examination there was little change, except for severe bradycardia and an irregular cardiac rhythm. An electrocardiogram showed auricular fibrillation. Digitalis was omitted, Quinidine was given, and after a short period of regular rhythm auricular flutter with varying degrees of heart block supervened and persisted. The venous pressure was now slightly elevated, measuring 130 mm of saline solution, and the circulation time (determined with paraldehyde and sodium cyanide) was prolonged. The vital capacity was unchanged. The total serum protein was now 10.42 Gm per hundred cubic centimeters, with albumin 4.85 Gm and globulin 5.57 Gm. Tests of hepatic function showed no impairment. Roentgenograms of the gastrointestinal tract were normal.

The patient remained afebrile throughout this period. After administration of digitalis was discontinued the pulse rate became normal. The muscular complaints persisted, and dyspnea was a prominent feature. There was little symptomatic improvement.

For several months following discharge the patient continued to take alpha tocopherol without benefit. Six months later he appeared slightly improved. He had gained 15 pounds (6.75 Kg) in weight. He still complained of severe dyspnea and a productive cough. For four months he had been taking large amounts of vitamin concentrates. The development of telangiectases on the palmar aspects of the hands was noted. An

electrocardiogram still showed deviation of the axis to the right and auricular flutter with variable block.

**CASE 2**—W. B., a 56 year old white carpenter, entered the hospital on Oct. 27, 1941. Since 1928 the patient had been followed in the outpatient clinic of this hospital for numerous complaints, and various diagnoses had included chronic sinusitis, chronic bronchitis, emphysema and arteriosclerotic heart disease. The earliest complaint referable to the present illness occurred in February 1941, when there was intermittent periorbital edema for several weeks. In March 1941 the patient had "influenza" with chills, fever, malaise and a sore throat, accompanied by generalized pains and stiffness of the muscles. The chronic cough which had been

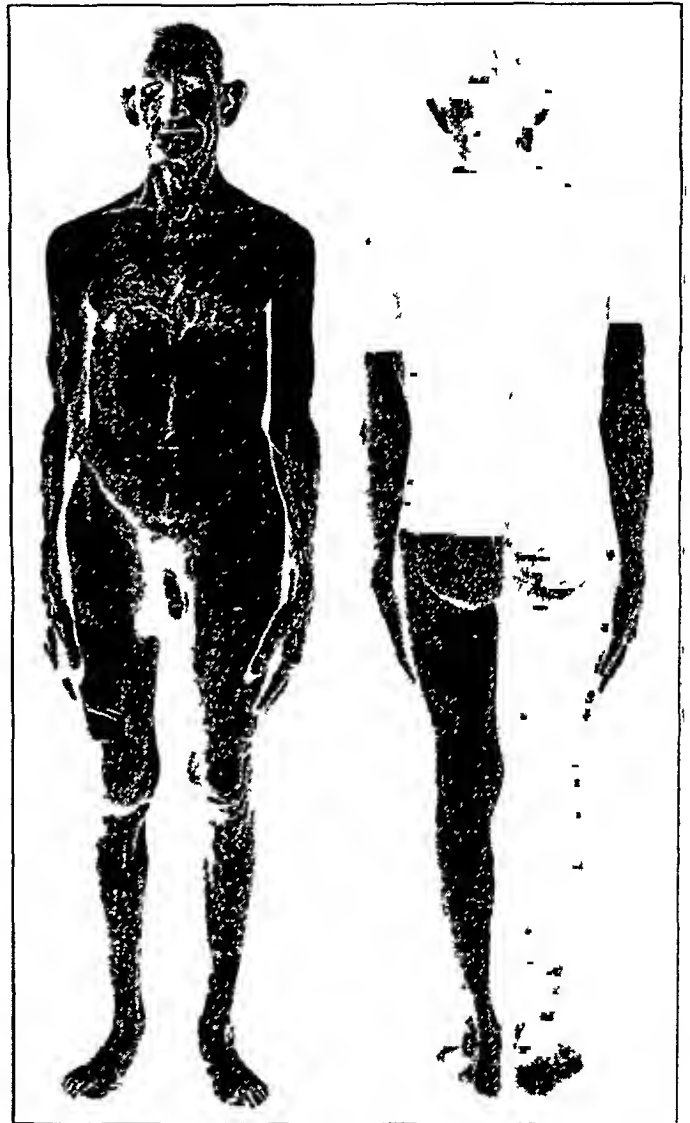


Fig 2 (case 2) —Muscular atrophy and pigmentation are present

present for years became more severe and productive of as much as 16 ounces (480 cc) of sputum daily. The acute febrile illness was of short duration. The muscular stiffness and soreness persisted, especially in the lower part of the back, legs and shoulders. He began to have cramps in the muscles, particularly at night, and also noticed occasional coarse twitching of the muscles. There was progressive loss of strength and of muscle substance, mainly in the buttocks and trunk. In May 1941 he first noted that after exposure to cold his hands became blue and painful. Shortly afterward he noted that cuts on the face and hands bled less profusely than formerly. This was followed by intermittent hoarseness, occasional double vision and difficulty in swallowing with occasional regurgitation of solid food. Dyspnea was

more severe with the present illness. There was an intermittent low grade fever. The weight fell from 156 to 126 pounds (70 to 57 Kg) in the year prior to admission.

*Physical Examination*—The patient was a poorly developed, emaciated man. There was no abnormality of the head and neck. The chest was emphysematous, with a low diaphragm. The lungs were clear. The heart was normal, and the blood pressure was not elevated. The peripheral vessels were sclerotic. The edge of the liver was palpable 4 cm below the costal margin. The spleen could not be felt. The skin was not thickened, and there was no rash. Although there was generalized muscular atrophy, this was most marked in the pelvic and shoulder girdles, calves and thighs. Weakness was more pronounced in the proximal portions of the extremities. There was tenderness in the pectoral muscles, the trapezius muscles and the calf muscles.

*Laboratory Studies*—There was no anemia. The total leukocyte count was not elevated, varying between 5,900 and 7,900 per cubic millimeter. The differential count showed 67 per cent neutrophils, 25 per cent lymphocytes and 8 per cent monocytes. The sedimentation rate was not elevated. Examinations of the stools and urine revealed nothing abnormal. The total serum protein was 7.3 Gm per hundred cubic centimeters, with albumin 5.01 Gm and globulin 2.30 Gm. The hippuric acid and bromsulphalein tests of hepatic function showed no impairment. Roentgenograms of the chest showed increased bronchovascular shadows at the bases of the lungs, and roentgenograms of the sinuses showed no abnormality. Bronchograms were normal. An electrocardiogram was normal. The basal metabolic rate was +1 per cent.

*Biopsy of the Quadriceps Muscle and Overlying Skin*—The skin showed atrophy of the epidermis and moderate lymphocytic infiltration into the perivascular connective tissue of the corium. The muscle showed a great increase in nuclei, degenerating muscle fibers undergoing phagocytosis and slight focal increase in connective tissue, which was infiltrated with moderate numbers of lymphocytes and histiocytes. The inflammatory reaction was most pronounced about the vessels.

*Course in the Hospital*—The first admission was for seventeen days. During this time the temperature and pulse rate were not elevated. No specific treatment was employed. Postural drainage was without effect. The patient was discharged Nov 13, 1941, without evident improvement.

After his discharge the productive cough continued and dyspnea increased. He noted progressive weakness of the forearms and hands, and the muscular stiffness, cramps and twitching persisted to such a degree that he was unable to work.

On Feb 23, 1942 he reentered the hospital for a period of ten days. There were no additional significant physical findings. The vital capacity was reduced, being 2.6 liters. The circulation times (measured with paraldehyde and sodium cyanide) were slightly prolonged, although there was no elevation of the venous pressure. Fluoroscopic examination of the chest showed poor excursion of the diaphragm and increased excursion of the thoracic cage. The patient did not improve. There was no fever. Oral administration of alpha tocopherol (40 mg daily) and of acetylsalicylic acid was instituted and continued after discharge from the hospital.

On April 18, six weeks after the second discharge, the patient reentered the hospital. The muscular symptoms, weakness and productive cough had persisted.

There was frequent periorbital edema, and difficulty in swallowing was greater. Three days prior to his admission respiratory distress became acute and obliged the patient to remain in bed. Pains in the muscles became severe. The patient now appeared severely dyspneic and cyanotic. Breathing was effected entirely by the accessory muscles of respiration. Small punctate erythematous lesions were present on the palate. There was a light brown scaly exfoliation of skin of the anterior abdominal wall. Muscular tenderness was generalized. The lungs were clear, and the heart was normal.

The patient was placed in an oxygen tent, where he remained for five days. During this period there were daily rises of temperature to 102 F. A roentgenogram of the chest showed the lungs to be clear. With the fever there was no leukocytosis, although the sedimentation rate was rapid. Several injections of neostigmine methylsulfate administered soon after his admission had no appreciable effect on the respiratory paralysis. The patient slowly improved and was discharged thirteen days after admission. By this time the respiratory difficulty had diminished.

*CASE 3*—L. D., a 65 year old white man, entered the hospital on Nov 25, 1940. For two years he had experienced dyspnea on exertion and increasing fatigability. In May 1939 an erythematous rash had appeared on his face. This was treated with roentgen therapy, after which it slowly disappeared. At the same time he began to have periorbital edema, particularly in the mornings. In November 1939 redness and swelling of the hands occurred, and these persisted. In September 1940 redness of the skin of the elbows was noted. For one year prior to admission the patient had had a chronic productive cough.

*Physical Examination*—The patient was well developed and well nourished. The skin of the face was thickened and reddened. Pitting edema of the face was present. Numerous telangiectases were present on the face, scalp, thorax and soft palate. The hands and wrists were swollen, with thickening and redness of the overlying skin. The chest was emphysematous. Rales were heard at the bases of the lungs. The heart was normal. The blood pressure was not elevated. The edge of the liver was felt 4 cm below the costal margin, and the spleen was not palpable. No tenderness or atrophy of muscles was observed.

*Laboratory Studies*—There was a slight normochromic, normocytic anemia, with hemoglobin 12.2 Gm. per hundred cubic centimeters. The total leukocyte count was 5,000 per cubic millimeter, with a differential count of 59 per cent neutrophils, 14 per cent lymphocytes, 26 per cent monocytes and 1 per cent eosinophils. The corrected sedimentation rate was not elevated. Examinations of urine and stools showed them to be normal. Roentgenograms of the long bones, spine, skull and chest were normal. The plasma protein was normal. Tests of renal and of hepatic function gave normal results.

*Biopsy of Skin and Muscle*—A section of skin showed slight perivascular lymphocytic infiltration of the corium. A section of muscle showed degenerative and proliferative changes of the fibers, with slight increase in interstitial tissue, occasional giant cells and focal interstitial collections of lymphocytes and histiocytes.

*Course in the Hospital*—During the seven day period of observation the temperature showed frequent rises to 99.6 F (oral). The patient was treated with parenteral injections of liver extract. There was no



clinical improvement, and no definite diagnosis was made

Subsequently there developed persistent stiffness and pain in the muscles, which were made worse by exercise. Chronic hoarseness appeared. Paresthesias occurred in the hands and feet. The swelling of the face and hands subsided after six months. Trophic ulcerations appeared on the knuckles. No Raynaud phenomena were observed. More telangiectases appeared on the skin. The weakness, dyspnea and chronic cough continued, however, the patient was subjectively improved after prolonged vacation.

On Nov 6, 1941, one year after the original admission, the patient returned for examination. He had lost 5 pounds (2.25 Kg) in weight during the year. The skin of the hands and the lower part of the forearms was rough and thickened, with a brownish red discoloration. A healing ulcer was present over an interphalangeal joint. The skin of the feet was erythematous and cool. There was no edema. The telangiectases, originally noted, persisted. Rales were present at the base of each lung posteriorly. The liver and spleen were not palpable. There was atrophy and weakness of the musculature of the shoulder girdle. No muscular tenderness was demonstrable.

The hemoglobin content and the total erythrocyte count were unchanged. The total leukocyte count was 5,200 per cubic millimeter, with a differential count of 60 per cent neutrophils, 20 per cent lymphocytes, 15 per cent monocytes and 5 per cent eosinophils. The corrected sedimentation rate was moderately elevated. An electrocardiogram was normal.

CASE 4—M B, a 35 year old white woman, a nurse, was seen in the hospital Jan 20, 1942. In September 1938, following extraction of a tooth, an abscess developed in the left side of the upper jaw, this continued to drain for three months. During this time she began to experience pains in the calves of her legs. In January 1940 painful, indurated vesicular lesions appeared on the fingers and dorsal aspects of the hands, these persisted for several months. There were repeated paronychias. The rash on the hands was followed by a painful red discoloration of the neck, which remained for three months and left a residual light brown pigmentation. In August 1941 the extensor surfaces of the thighs were covered with a painful erythematous rash, which persisted for several months. This was followed by a symmetric erythema of the face and a scarlatiniform eruption involving the shoulders, axillary folds and elbows. This rash disappeared after several months, leaving a residual brownish discoloration and flaky desquamation.

For one year prior to examination the patient's face had been swollen, particularly in the mornings. For six months she had observed that her hands and forearms became blue and painful following exposure to cold. Intermittent painless swelling of the hands occurred. A feeling of numbness was frequently present in the extremities. There was dyspnea on exertion. For two months there were severe pain, tenderness and stiffness of the muscles of the arms and shoulder girdle. There were frequent nocturnal cramps of the quadriceps muscles, and fibrillary twitchings were noted in the muscles of the right thigh. Recently the patient had become aware of thickening of the skin of the face and increased axillary sweating. The appetite had remained good, and there had been no loss of weight. For six weeks the patient had been taking large amounts of alpha tocopherol by mouth, without benefit except for a decrease in the numbness of the hands and feet.

The past history included an attack of pyelitis in 1935. In September 1939 the patient had a spontaneous abortion of six weeks. In September 1940 an eight month pregnancy terminated in a stillbirth. During the past year the menstrual flow had diminished in amount.

*Physical Examination*—The patient was well developed and well nourished. There was light brown pigmentation of the skin of the cheeks, neck and anterior axillary folds. The fingers showed fusiform swelling, and the overlying skin was shiny and atrophic and in places was adherent to underlying tissues. There was a blotchy red discoloration of the hands, with focal areas of depigmentation. A single trophic ulcer was present. There was moderate periorbital edema. The isthmus and the right lobe of the thyroid were diffusely enlarged. The heart and lungs appeared normal. Tenderness was marked in the muscles of the arms and was less severe in the muscles of the shoulder girdle and forearm. There was no muscular atrophy.

*Laboratory Studies*—There was no anemia. The total leukocyte count was 5,400 per cubic millimeter, with 46 per cent neutrophils, 46 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. The sedimentation rate was not elevated. The urine was normal. An electrocardiogram was within normal limits. Fluoroscopic examination of the chest showed good excursion of the diaphragm. The total serum protein was 7.19 Gm per hundred cubic centimeters, with albumin 4.33 Gm and globulin 2.86 Gm. The basal metabolic rate was normal (—8 and 5 per cent).

CASE 5—J J, a 51 year old white farmer, entered the hospital on Oct 6, 1941. Eight months previously he had a "cold" characterized by a sore throat, nasal discharge and vague muscular pains. Ten days later his face, hands and ankles became swollen. The swelling continued for six weeks and thereafter recurred intermittently. Several months later he noticed pain and stiffness of the muscles of the extremities. These were most severe in the mornings and were relieved by gentle exercise but aggravated by moderate or severe exertion. One month before admission to the hospital he first noticed thickening and pigmentation of the skin of the extremities and later of the entire body. There was a progressive loss of strength and a loss of 27 pounds (12 Kg) of weight during the present illness. No Raynaud phenomena were noted.

*Physical Examination*—The patient was poorly nourished and appeared chronically ill. There was a uniform dusky brown pigmentation of the skin except for an area of bluish brown discoloration over the thoracic and lumbar regions of the spine. There were splotchy areas of depigmentation of the face, forearms and hands. The skin of the entire body was thickened and adherent to underlying structures. Thickening was most pronounced in the face, distal portions of the extremities and scrotum. There was moderate diffuse muscular atrophy but no demonstrable muscular tenderness. Because of the thickened skin, motion of the fingers, wrists, elbows, ankles and knees was limited. The remainder of the examination failed to show anything abnormal.

*Laboratory Studies*—There was no anemia. The total leukocyte count was 16,600 per cubic millimeter, and subsequent determinations showed little change. Differential counts showed an increase in neutrophils without any increase in monocytes or eosinophils. The sedimentation rate of the blood was persistently elevated. Examinations of the urine and stools gave normal results. Roentgenograms of the hands and

feet showed no abnormality, while one of the chest showed apical fibrosis. The serum cholesterol (during fasting) was 161 mg per hundred cubic centimeters. The serum protein and the albumin and globulin were normal. The basal metabolic rate was moderately elevated on three occasions (+25, +15 and +11 per cent).

*Biopsy of the Quadriceps Muscle and Overlying Skin*—The skin showed extreme thickening and hyalinization of the corium, with perivascular lymphocytic infiltration. The muscle showed a moderate increase in the number of nuclei and slight infiltration of the interstitial tissue with lymphocytes and histiocytes. A few necrotic muscle fibers appeared to be undergoing phagocytosis.

*Course in the Hospital*—The patient was observed for three weeks. The temperature was frequently elevated to 100 F (oral), and the pulse rate varied between 70 and 100. Various therapeutic procedures

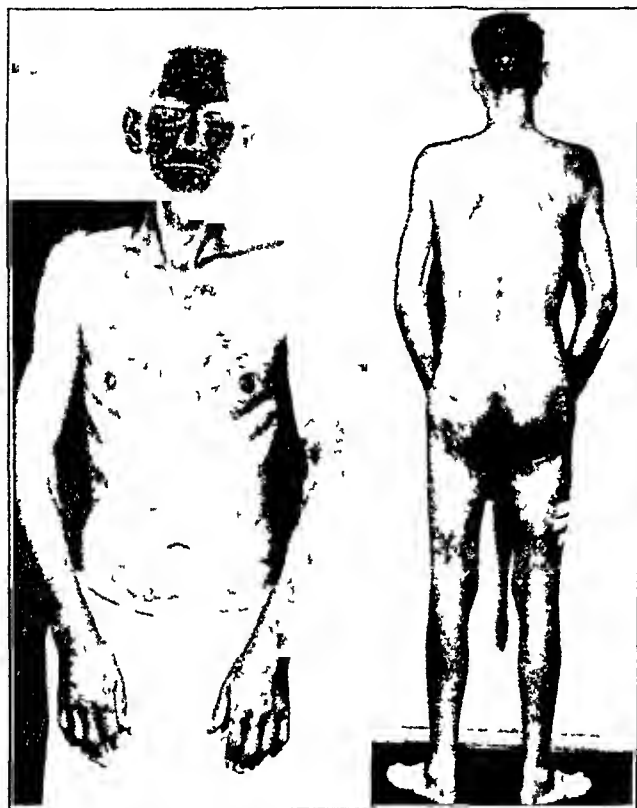


Fig 3 (case 5)—Pigmentation may be seen over the spine

were employed. Warm baths and fever therapy with typhoid vaccine were ineffective. Local application of methyl salicylate gave no relief. An attempt to produce cutaneous vasodilatation with intravenous administration of a saline solution containing 3 mg of histamine gave no response. Likewise 1 Gm of nicotinic acid given intravenously had no effect on the cutaneous temperature. There was no clinical improvement. At the time of discharge the patient was instructed to take 4 Gm of potassium iodide daily. One month later his status was unchanged.

**CASE 6**—R W, a 52 year old white man, entered the hospital on March 29, 1942, complaining of dyspnea and muscular pains. Five years previously he had an episode of severe substernal pain which persisted for five hours. He was told then that he had hypertension. Thereafter he had dyspnea on exertion, paroxysmal nocturnal dyspnea, a chronic productive cough and occasional precordial pain. In 1940 he had an opera-

tion for a strangulated abdominal hernia, and several months later, an operation for an inguinal hernia. After the second operation and approximately eighteen months prior to his admission to the hospital, there was a gradual onset of muscular pains and stiffness, which were more severe in the arms than in the legs. Simultaneously, a blotchy erythematous eruption appeared on the trunk. This rash never caused any discomfort and disappeared and recurred intermittently during the next eighteen months. The muscular stiffness and soreness persisted in the extremities and were relieved slightly by acetylsalicylic acid. There were occasional paresthesias in the lower extremities and frequent nocturnal cramps in the muscles of the legs. For at least one year there had been periorbital edema, particularly in the morning. Hoarseness was a troublesome symptom during the present illness. There was no loss of weight.

*Physical Examination*—The patient was an obese, dyspneic elderly man. He had slight cyanosis of the nail beds. The retinal arteries showed sclerotic changes. The chest was emphysematous. There were numerous moist rales over the lower portion of each lung posteriorly. The heart was slightly enlarged and had a regular rhythm. The blood pressure was 150 systolic and 105 diastolic. The liver and spleen were not enlarged. There was no edema. Tenderness to deep pressure was elicited over the trapezius muscles and the muscles of the upper parts of the arms, thighs and calves. There was no atrophy of muscles. Neurologic examination gave negative results. Over the thorax there were several pink maculopapular lesions which measured 3 cm in diameter. One similar lesion was present on the right elbow.

*Laboratory Studies*—The hemoglobin content was 10 Gm per hundred cubic centimeters. The erythrocyte count was 3,000,000 per cubic millimeter, and the total leukocyte count, 8,700, with a normal differential count. The corrected sedimentation rate was elevated. The urine was normal. The total serum protein amounted to 9.70 Gm per hundred cubic centimeters, with albumin 2.91 Gm and globulin of 6.79 Gm. The basal metabolic rate was +17 per cent. A roentgenogram showed slight enlargement of the heart and congestive changes at the bases of the lungs. An electrocardiogram showed small T waves in all leads and slurring of the QRS complexes in leads 2 and 3.

*Biopsy of the Quadriceps Muscle and Overlying Skin*—The skin showed atrophy of the epidermis with loss of appendages. In the section of muscle there were characteristic proliferative and degenerative changes of the fibers, with collections of lymphocytes and histiocytes in the interstitial tissue, mainly about the vessels.

*Course in the Hospital*—The patient was digitalized and given salicylates. The dyspnea diminished, and the pulse rate became normal. There was no fever. He was discharged after nine days. Several weeks later he was examined again. There was a papular pink rash on the trunk and extremities. On the forearms the rash tended to form circinate lesions. Muscular tenderness persisted.

**CASE 7**—W H, a 61 year old white farmer, was well until five weeks prior to his admission to the hospital, when there was a sudden onset of severe aching pain in the back of the neck and mild sore throat. Within a few hours pains occurred in the shoulders, upper extremities and abdomen and to a lesser extent in the lower extremities. The patient was obliged to go to bed, where he remained. In the muscles and



joints there were constant pain and stiffness, which were worse in the morning. There were intermittent swelling and redness of the fingers and toes. The sore throat persisted. Five days before admission, chills, fever and sweats developed. Throughout the entire five week period there was anorexia, and the patient lost 20 pounds (9 Kg) in weight. No rash was observed. The patient experienced slight hoarseness and dysphagia and attributed these symptoms to his sore throat.

Ten years prior to admission the patient had measles followed by a mild chronic cough. During this period there were also occasional asthmatic attacks, particularly during the summer.

*Physical Examination*—The patient appeared poorly developed and poorly nourished and chronically ill. The teeth were carious. The pharynx was slightly injected. Examination of the heart and lungs revealed nothing remarkable. The edge of the liver was felt 5 cm below the costal margin. The spleen was not palpable. There were slight atrophy of the muscles of the extremities and generalized exquisite muscular tenderness. The joints were not swollen, however, pressure over the joints of the shoulder and wrist elicited tenderness.

*Laboratory Studies*—There was no anemia. The total leukocyte count was 10,000 per cubic millimeter, with a normal differential count. The corrected sedimentation rate was elevated, being 34 and 42 mm per hour on two determinations. A roentgenogram of the right shoulder joint showed no abnormality, and one of the spine showed hypertrophic arthritis in the cervical region. In the initial electrocardiogram there was an intermittent sinoauricular block. Subsequent tracings showed normal sinus rhythm. The blood uric acid was 2.6 mg per hundred cubic centimeters. Cultures of material from the throat did not yield pathogenic organisms. The patient's serum did not agglutinate *Brucella abortus* organisms. The total protein and the album-globulin ratio were normal. The basal metabolic rate was  $-2$  per cent.

*Biopsy of the Deltoid Muscle*—There were a pronounced increase of muscle nuclei and a moderate inflammatory response in the interstitial connective tissue. Many muscle fibers showed degenerative changes.

*Course in the Hospital*—The patient was observed for eleven days. On the first and the second day the temperature rose to 99.6 F, and thereafter it remained normal. The pulse rate was not elevated. Determinations of the vital capacity, venous pressure and circulation times (sodium cyanide and paraldehyde) revealed normal values. On the third day salicylate therapy was begun, and this resulted in great improvement. The patient became ambulatory within a week. Muscular stiffness and tenderness persisted but were less severe.

When examined one month later, the patient still complained of muscular stiffness and slight tenderness of the muscles, but there was no swelling or tenderness of the joints. He had gained 10 pounds (4.5 Kg) in weight.

CASE 8—M. C., a 32 year old white woman, entered the hospital on May 1, 1942. In December 1940 she first noticed vague pains in muscles and joints. In March 1941, after extraction of many teeth, she had fever, with a temperature of 102 F, slight dyspnea, orthopnea and edema. The edema began in the lower extremities and slowly spread to involve the trunk and upper extremities but did not affect the face. There

were no urinary complaints. At this time her local physician found fever, edema, an apical systolic murmur and tenderness of joints. He made a diagnosis of acute rheumatic fever and treated the patient with salicylates and digitalis in addition to rest in bed. The edema, dyspnea and orthopnea subsided within six weeks. At this time the patient began to have frequent frontal headaches and severe pains in the muscles of the left arm and forearm and in the left shoulder and elbow joints. The pains were made worse by motion, and the patient remained in bed. She continued to have an intermittent slight fever, weakness and malaise. There was occasional edema of the hands. No swelling of the joints was observed. A painless erythematous papular rash occurred intermittently about the mouth. The appetite remained good, and the patient gained 10 pounds (4.5 Kg) in weight during the present illness.

*Physical Examination*—The patient appeared well developed and well nourished. The heart was not enlarged. A rough basal and a soft apical systolic murmur were present. The liver and spleen were not enlarged. A few small red papular lesions were present about the mouth. Pain was produced by pressure over the left shoulder joint. There was muscular tenderness over the left arm and forearm, over the upper portion of the left leg and to a lesser extent in the left pectoral region. These pains were increased by motion. There was no limitation of motion and no swelling of the joints. The hands and feet showed slight puffiness.

*Laboratory Studies*—On the patient's admission the hemoglobin content was 12.3 Gm per hundred cubic centimeters and the total erythrocyte count 4,460,000 per cubic millimeter and the total leukocyte count 12,250. Differential leukocyte counts were not remarkable. The sedimentation rate was not elevated. Examination of the urine and stools showed them to be normal. The total serum protein and the albumin-globulin ratio were normal. An electrocardiogram showed no abnormality. A roentgenogram of the chest was normal, as were films of the left knee and the adjacent long bones. Culture of material from the throat showed no pathogenic organisms. Cultures of the urine and blood were sterile. Agglutination tests of the patient's serum with *Br. abortus* and *Pasteurella tularensis* gave negative results.

*Biopsy of the Deltoid Muscle*—The muscle showed a moderate increase in sarcolemmal nuclei and a moderate inflammatory reaction in the interstitial connective tissue. Phagocytosis of fibers was not observed.

*Course in the Hospital*—During the two week period of hospitalization the muscular pains persisted, although they varied in location and severity. On several occasions during the first week there were rises in temperature to from 99.6 to 100 F, and the pulse rate varied between 90 and 110. Thereafter the pulse rate and the temperature were normal. Determinations of the venous pressure, circulation time and vital capacity revealed them to be within normal limits. Digitalis was discontinued. Large amounts of salicylates did not relieve the muscular pains. The frontal headaches persisted. The patient was encouraged to become ambulatory. It was observed that walking short distances fatigued her but did not cause dyspnea. At the time of discharge she was instructed to take frequent warm baths and 30 mg of alpha tocopherol (orally) daily. Her weight fell from 134½ to 125½ pounds (60.5 to 56.5 Kg) while she was in the hospital.

One month after discharge the patient was examined again. At this time her muscular pains and exertional

dyspnea persisted and there was a loss of 8 pounds (3.6 Kg) of weight. There was definite periorbital edema. Additional laboratory studies showed no change.

**CASE 9**—L. S., a 44 year old white farmer, was first seen in the outpatient clinic of the hospital in September 1938. At that time he complained of chronic headaches and postnasal discharge. The diagnosis of sinusitis was confirmed by roentgenograms. Following treatment the sinusitis appeared to be relieved but the headaches were not affected. A psychiatric consultant was of the opinion that the patient had a schizoid personality and that the headaches were functional. The patient was not seen again until April 9, 1942, when he entered the hospital complaining of pains in muscles and joints of five months' duration. In November 1941 a dull aching pain appeared in the right shoulder and extended down the right arm. This pain, which was aggravated by motion, subsided within several weeks, and similar pain developed in the left arm. Within a month incapacitating stiffness and soreness involved the entire skeletal musculature. In March 1942 the patient first noticed that his hands and feet would become blue and painful after they were exposed to cold. At the same time there occurred edema of the hands, wrists, feet and ankles, and this was present intermittently thereafter. In addition, there were pains in the joints of the shoulders, wrists and toes. There was no appreciable loss of weight or strength.

**Physical Examination**—The patient was well developed, well nourished and muscular. The skin was clear. The retinal arteries were slightly sclerotic. The heart and lungs were normal. Muscular tenderness to pressure was present over the right pectoral region, the posterior axillary folds and the trapezius muscles. There were no other abnormal physical findings.

**Laboratory Studies**—There was no anemia. The total leukocyte count was 4,700 per cubic millimeter, with a normal differential count. Examination of the urine gave normal results. The sedimentation rate was slightly elevated on two of three determinations. An electrocardiogram was normal. Roentgenograms of the hands showed no abnormalities. The basal metabolic rate was normal. The total serum protein amounted to 7.84 Gm per hundred cubic centimeters, with albumin 4.06 Gm. A biopsy of the deltoid muscle showed no abnormality.

**Course in the Hospital**—In the ten day period during which the patient was observed, the pulse and temperature remained normal. The stiffness, soreness and tenderness of muscles persisted and were not relieved by acetylsalicylic acid. While in the hospital the patient lost 7½ pounds (3.4 Kg) in weight.

The patient reentered the hospital two months after the first admission. He had continued to have severe persistent muscular pains, which interfered with sleep. There was a loss of 20 pounds (9 Kg) of weight. The complaints were otherwise unchanged.

On examination diffuse muscular tenderness was noted. The patient was unable to abduct his arms to a horizontal position because of weakness and pain. There was definite atrophy of the musculature of the shoulder girdle and upper parts of the arms. The laboratory findings showed no appreciable change.

**Biopsy of the Quadriceps Muscle**—In contrast to the previous section of deltoid muscle, this section showed pronounced changes. There were extensive sarcolemmal nuclear proliferation and extensive but variable degenerative changes in the muscle fibers. There was a moderate inflammatory reaction in the interstitial

The patient remained in the hospital several weeks and was not improved by artificial fever therapy induced by typhoid vaccine, by frequent hot baths or by oral administration of 40 mg of alpha toopherol daily.

#### COMMENT

There are certain interesting features in the cases of this small series of patients, 7 male and 2 female. Their ages ranged from 32 to 61 years. A febrile illness initiated the earliest symptoms in 2 cases, and in 2 the earliest symptoms followed recent dental extractions. The duration of the illness prior to establishment of the diagnosis varied from five weeks to eight years. Only for 1 patient (case 4) was the diagnosis of dermatomyositis made prior to admission to the hospital.

Cutaneous manifestations occurred in 7 of the 9 cases. In 5 instances there was an erythematous rash, which varied in extent, location and duration. In 4 cases there were sclerodermatous changes, which were diffuse in 1 case and in the others localized to the extremities or to the face and extremities. Focal blue-brown pigmented areas were present over the spine in 2 cases. Hyperhidrosis was noted in 1 instance. Trophic ulcers of the hands were noted in 2 patients with sclerodermatous changes. Telangiectases were prominent in 2 cases. One patient exhibited punctate erythematous lesions of the soft palate, and a second had numerous telangiectases on the palate. Edema, which most commonly occurred in the periorbital region, was present in every case.

Evidence of involvement of muscles was a constant finding. Every patient complained of muscular stiffness which was pronounced in the morning and was usually relieved by gentle exercise and made worse by prolonged or severe exertion. Subjective muscular weakness was absent in only 1 case. Three patients complained of muscular cramps which tended to be more severe at night. Three patients noticed spontaneous twitching of their muscles. Palpation of the muscles, particularly of the shoulder girdle group, elicited tenderness in every case except 1 (case 3). The consistence of the muscles was normal or reduced. In 6 patients there was demonstrable muscle atrophy, which affected most often the musculature of the shoulders and of the pelvic girdle. Involvement of nonskeletal striated muscle was less frequent. Hoarseness occurred in 4 instances, dysphagia in 2 and diplopia in 1. Six patients complained of dyspnea. In several instances other factors, such as emphysema and cardiac failure, may have produced this symptom. Fluoroscopic evidence of impairment of the motion of the diaphragm

was noted in 2 cases. Two patients had cardiac arrhythmias, which might be considered incidental findings or evidence of cardiac involvement in this disorder. In a third instance (case 6) evidence of myocardial disease preceded any symptoms referable to dermatomyositis.

A history of Raynaud phenomena was elicited in 4 cases. In 2 of these the patients had sclerodermatous changes of the hands. In a fifth case, in which the patient had diffuse scleroderma (case 5), there was no history of Raynaud phenomena yet they were readily demonstrated by temperature experiments.

Fever, usually slight, was present in 5 of the cases during the illness. Loss of weight was present in 7 cases and varied from 10 to 100 pounds (4.5 to 45 Kg). Three patients had a chronic productive cough, which might have been secondary to disturbance of the respiratory muscles in 2 of them. Three patients complained

with the hemoglobin content varying from 10 to 12 Gm per hundred cubic centimeters. In 7 of the 9 cases the leukocyte count was within normal limits, while in 2 cases it was elevated on repeated determinations. In the differential counts 5 per cent and 6 per cent eosinophils respectively were noted in 2 cases on single determinations, but in subsequent differential counts eosinophils were less numerous. In the remaining cases there was no eosinophilia. In 3 cases there were 8 per cent or more monocytes, and in 1 of these the monocyte count varied between 15 and 26 per cent. A moderate increase in the sedimentation rate was observed in 5 cases. Repeated examinations of urine and stools showed no abnormality in any case.

In every instance the plasma nonprotein nitrogen was normal. Determinations of the serum calcium, phosphorus and phosphatase showed them to be normal in every case. Blood

TABLE 1—Representative Laboratory Values\*

Studies of Blood																	Studies of Urine				
Case No	Red Blood Cells, Mil lions	Hemo globin, Gm per 100 Cc	White Blood Cells	Differential Count, per Cent				Corrected Sedimenta tion Rate,† Mm / Hr	Serum Protein		Choles terol, Mg per 100 Cc	Sugar, Mg per 100 Cc	Mg Crea tine per 24 Hr	Mg Creat inine per 24 Hr	Creat inine Coeffi cient	Num ber of Deter mina tions					
				Neu tro phils	Eosino phils	Mono cytes	Lym pho cytes		Albu min, Gm per 100 Cc	Glob ulin, Gm per 100 Cc											
1	4 33	12 7	10,600	70	6	6	17	30	3 91	4 10	178	80	155	700	12 3	9					
2	4 6	12 8	6,000	66	0	8	25	12	5 01	2 30	238	70	365	519	9 6	5					
3	3 7	10 9	4,800	76	0	6	18	19	5 08	2 38	143	100									
4	3 63	12 0	5,400	46	2	6	46	14	4 33	2 86		108	247	928	15 5	1					
5	4 6	11 6	15,000	72	2	3	21	28	4 10	3 06	161	90	330	944	17 0	3					
6	3 7	10 2	8,700	65	0	2	33	28	2 91	6 78	151		320	1,050	10 5	1					
7	5 1	13 0	10,000	75	3	2	18	34	3 85	4 06		76	633	347	6 2	1					
8	4 46	12 3	12,250	80	3	1	16	26	4 67	1 86		108	81	292	5 0	2					
9	5 04	15 2	4,600	71	0	2	26	12	4 06	3 78		98	300	903	12 4	2					

\* For blood counts and blood chemistry only single illustrative values are cited. For creatine and creatinine, average values are given.

† Wintrobe method.

of paresthesias. There was slight to moderate enlargement of the liver in 4 cases. Three patients had arthritic pains without localized swelling of the joints.

Retinal changes, splenomegaly, enlargement of lymph nodes, serous effusions, hemorrhagic disorders and neurologic disturbances were not observed in this series.

Therapy in these 9 cases met with little success. Oral administration of salicylates gave symptomatic relief in only 1 instance. Frequent hot baths gave temporary relief. Alpha tocopherol given orally in doses of 40 mg daily was employed for periods of one to several months in 5 cases without significant relief. Fever therapy with typhoid vaccine gave slight improvement in 1 case but not in 2 others. Other measures were ineffective.

Few abnormal laboratory findings were present in this series. In 4 of the 9 cases there was a moderate normocytic, normochromic anemia,

sugar values (fasting) varied between 76 and 108 mg per hundred cubic centimeters. Two patients exhibited slight elevations of the basal metabolic rate, with repeated determinations showing values between plus 10 and plus 25 per cent, while the rates of the remaining 7 patients were normal. The serum cholesterol was normal in the 5 cases in which it was determined, as was the serum chloride in the 3 cases in which it was determined. The Kahn reaction of the blood was negative in every instance. In 2 of the 9 cases the plasma protein was in excess of 8 Gm per hundred cubic centimeters. The hyperproteinemia resulted from an increase in the globulin fraction. In a third case a slight decrease in the serum albumin together with a rise in the serum globulin resulted in a reversal of the albumin-globulin ratio. Examination of the spinal fluid, which was performed in 4 cases, showed no abnormality. Roentgenograms of the hands and feet and of the adjacent long bones showed no

abnormality in the 6 patients who had these studies

Anemia and significant leukocytosis or leukopenia are unusual in dermatomyositis.<sup>13</sup> A relative increase in the number of monocytes was present in approximately 50 per cent of a large series of cases reported by Schuermann,<sup>1b</sup> while in 45 per cent there was a significant eosinophilia. The sedimentation rate of the blood is frequently increased, especially during an acute exacerbation.<sup>1b</sup> Albuminuria was present in 14 of the 40 cases of O'Leary and Waisman,<sup>1a</sup> and in a small number of these the urinary sediment contained erythrocytes and casts. The basal metabolic rate usually has been found normal but may be elevated.<sup>4b</sup> Changes in the plasma proteins are infrequent. O'Leary and Waisman<sup>1a</sup> noted that in 2 of 4 cases the serum protein was reduced without change in the albumin-globulin ratio. In several instances<sup>11</sup> cases have occurred in which the concentration of serum proteins has been normal or reduced and there has been reversal or a tendency to reversal of the albumin-globulin ratio. In a case of poikilodermatomyositis, Horn<sup>15</sup> found hyperproteinemia due to an increase in the globulin fraction. The studies of blood calcium and phosphorus usually have shown no abnormality, although the serum calcium was low in a case described by Richter.<sup>16</sup> Osteoporosis has been observed.<sup>17</sup> Other laboratory findings usually have been normal. Milhorat and his co-workers<sup>12</sup> noted a disturbance in the ratio of urinary calcium to fecal calcium in dermatomyositis.

Determinations of creatine and creatinine in twenty-four hour specimens of urine were made in 8 of the 9 cases. Multiple determinations were made in 5 cases. In every instance there was spontaneous creatinuria, the amount varying from 53 to 633 mg per twenty-four hours. The percentage of creatine to total creatinine (preformed creatinine and creatine) varied from 10 to 65 per cent, with an average of 31 per cent. The amount of preformed creatinine was reduced in every case. The creatinine coefficient (number

of milligrams of creatinine excreted in twenty-four hours per kilogram of body weight) was reduced in all the male patients, being below 18 (normal range is 18 to 32), it was within normal limits in 1 female patient (15.5) and reduced in the other (5 [normal for females 9 to 26]).

The determinations of creatine and creatinine for these patients were carried out while the patients were on diets containing 60 to 80 Gm of protein daily. Bodansky and his co-workers<sup>18</sup> in a case of "generalized myositis fibrosa" found the degree of creatinuria with an ordinary diet to be identical with that noted with a creatine-free diet, although a high protein diet increased the amount of urinary creatine. This same observation was made by one of us in a case of dermatomyositis which was studied elsewhere and is not included in this group. Healthy women, particularly during the menstrual period may excrete considerable amounts of creatine<sup>19</sup>, hence the finding of this substance in the urine of women may not be abnormal. Many observers have noted creatinuria in dermatomyositis. We have found no case mentioned in which studies of creatine were made in which there was not creatinuria. The great daily variations in output of creatine and creatinine which occurred in our patients has also been observed by others.<sup>20</sup> In general, the degree of creatinuria increases with the activity of the disease. Milhorat and his co-workers<sup>12</sup> observed in 2 cases of dermatomyositis that administration of wheat germ oil resulted in a decrease in urinary creatine and an increase in creatinine. In 2 instances (cases 1 and 9) prolonged administration of vitamin E had no significant effect on excretion of creatine and creatinine. In the other cases this effect was not studied.

Ergographic tracings of the combined action of finger and forearm muscles were obtained in all cases and revealed apparently normal types of fatigue curves but diminished muscular power. The degree of loss of power varied with the severity of the case. Dynamometer studies of the hand grip and of the ability of retraction of the shoulder muscles showed diminished power when contrasted with that of other subjects of the

13 O'Leary and Waisman<sup>1a</sup> Schuermann<sup>1b</sup>

14 Lane, C W. Dermatomyositis, *South M J* **31** 287-294 (March) 1938. Kinney and Maher<sup>1c</sup> Keil<sup>4c</sup>

15 Horn, R C, Jr. Poikilodermatomyositis. Report of Case with Complete Postmortem Examination, *Arch Dermat & Syph* **44** 1086-1097 (Dec) 1941

16 Richter, R. Exfoliative generalisierte Erythrodermie bei Dermatomyositis, *Dermat Wchnschr* **111** 710-712 (Aug 17) 1940

17 (a) Griffiths, W J. Biochemical Aspects of Dermatomyositis, *Brit J Dermat* **52** 295-304 (Oct) 1940. (b) Kinney and Maher<sup>1c</sup> (c) Milhorat, Weber and Toscani<sup>12</sup>

18 Bodansky, M, Schwab, E H, and Brindley, P. Creatine Metabolism in a Case of Generalized Myositis Fibrosa, *J Biol Chem* **85** 307-325 (Dec) 1929

19 Smith, O W. Creatinine Excretion in Women. Data Collected in the Course of Urinalysis for Female Sex Hormones, *J Clin Endocrinol* **2** 1-15 (Jan) 1942

20 Dilger, M. Stoffwechseluntersuchungen bei Dermatomyositis, *Ztschr f Kinderh* **58** 564-573, 1936. Steinitz, H, and Steinfeld, F. Untersuchungen zum Kreatinstoffwechsel bei Dermatomyositis, *Ztschr f d ges exper Med* **79** 319-328, 1931. Griffiths<sup>17a</sup>

same age and sex. Loss of strength of the shoulder muscles was more pronounced than that of the hand muscles in all cases.

In 5 cases electrical stimulation of multiple muscle motor points failed to show the reaction of degeneration. In every instance, however, the amount of current necessary to produce contractions was 25 to 40 per cent greater than that required for controls. Somewhat similar observations have been made by others.<sup>21</sup> In 1 case (case 2), the muscle action current in response to single, paired and multiple nerve stimuli was studied with a cathode ray oscillograph by Harvey according to the method of Harvey and Maisland.<sup>22</sup> The muscle action current showed reduced voltage, but no other abnormality could be found.

In 6 cases studies were made of the carbohydrate metabolism. In 3 of these the dextrose tolerance test (oral) and the insulin tolerance test<sup>23</sup> were found to give normal results, in the other 3 these tests were not done. In all 6 cases the combined insulin and dextrose tolerance test as recommended by Himsworth<sup>24</sup> was employed. This procedure involves determination of simultaneous arterial (capillary) and venous sugar levels thirty and sixty minutes after oral administration of 50 Gm. of dextrose and intravenous injection of 5 units of insulin. Griffiths<sup>17a</sup> found that in some cases of dermatomyositis there was little difference between the arterial and the venous sugar values, particularly at thirty minutes, in contrast to results for normal persons, whose arterial sugar values are considerably greater than the venous levels. This diminished arteriovenous difference in dermatomyositis was interpreted as resulting from impaired glycogenesis in muscles under the influence of insulin. How-

ever, the 6 patients in our series failed to exhibit such a response. In every case a considerable arteriovenous difference was obtained. We employed this same test for patients with periaortitis nodosa, amyotrophic lateral sclerosis, myasthenia gravis, thyrotoxicosis, progressive muscular atrophy and myotonia dystrophica. All these had pathologic changes in the striated muscle, confirmed by biopsy. Only a single patient, one with marked hyperthyroidism, had values which might indicate reduction of the ability of muscles to form glycogen.

Studies of cutaneous temperature were made on 8 of the 9 patients. Measurements were made with a thermocouple which was sensitive to 0.5 degree (0.9 F) C. The response of the index finger to overcooling was abnormal in 5 of the cases. Lewis<sup>25</sup> has found that if a finger or a finger and a portion of the hand are immersed in water at 0 to 10 C for ten minutes vasodilata-

TABLE 2—Values for Arterial and Venous Sugar Obtained in the Combined Insulin and Dextrose Tolerance Test

Case	Fasting		30 Minutes		60 Minutes	
	Arterial *	Venous	Arterial *	Venous	Arterial *	Venous
1	108	96	79	53	87	74
2	144	150	188	114	160	110
5	104	100	110	86	137	119
7	80	78	105	92		
8	108	120	230	202	410	360
9	101	112	230	156	127	110

\* Arterial (capillary) blood sugar

tion of the exposed skin occurs during the immersion. After its withdrawal the finger recovers its original temperature within twenty minutes and then rises 1 to 6 degrees C (1.8 to 11 degrees F) above its original temperature and above that of the nonimmersed fingers. This elevation persists for many minutes. This is known as the reaction to overcooling and always occurs in normal subjects. Rarely the immersed forearm also shows the reaction to overcooling. In cases of severe Raynaud's disease, with or without diffuse scleroderma, Lewis observed that after immersion the chilled finger had a delayed and often incomplete return to its initial tempera-

21 Radermecker, M. A. Sur une forme chronique a evolution fatale de la dermatomyosite avec scleroderme, *J. belge de neurol et de psychiat* **40** 83-97 (Feb.) 1940. Hendry, A. W., and Anderson, T. E. Dermatomyositis, *Lancet* **1** 80-82 (Jan 14) 1939. Sheldon, J. H., Young, F., and Dyke, S. C. Acute Dermatomyositis Associated with Reticulo-Endotheliosis with a Note on Histological Findings, *ibid* **1** 82-84 (Jan 14) 1939. Karelitz and Welt<sup>2b</sup>. Marcus and Weinstein<sup>4b</sup>.

22 Harvey, A. M., and Maisland, R. L. Method for Study of Neuromuscular Transmission in Human Subjects, *Bull. Johns Hopkins Hosp* **68** 81-93 (Jan) 1941.

23 Fraser, R. W., Albright, F., and Smith, P. H. Value of Glucose Tolerance Test, Insulin Tolerance Test, and Glucose Insulin Tolerance Test in Diagnosis of Endocrinologic Disorders of Glucose Metabolism, *J. Clin. Endocrinol* **1** 297-306 (April) 1941.

24 Himsworth, H. P. Diabetes Mellitus: Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, *Lancet* **1** 127-130 (Jan 18) 1936.

25 (a) Lewis, T. Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers. A Variety of Raynaud's Disease, *Heart* **15** 7-101 (Aug.) 1929. (b) Observations upon the Reactions of the Vessels of the Human Skin to Cold, *ibid* **15** 177-208 (May) 1930. (c) Lewis, T., and Landis, E. M. Further Observations upon a Variety of Raynaud's Disease, with Special Reference to Arteriolar Defects and to Scleroderma, *ibid* **15** 329-350 (July) 1931. (d) Lewis, T. Supplementary Notes upon the Reactions of the Vessels of the Human Skin to Cold, *ibid* **15** 351-358 (July) 1931.



ture with the subject at ordinary room temperature. Even in such cases the reaction to overcooling occurred if the room temperature was sufficiently high (e. g. 30 C).

Eight patients and 10 normal controls had one forearm and hand immersed in water at 0 C for three minutes. Prior to the immersion the subjects were allowed fifteen to thirty minutes to attain equilibrium with the room temperature at which the observations were made. During this period frequent measurements of temperature were made at selected areas. No measurements were made while the hand and forearm were immersed. After withdrawal, the forearm and hand were dried by gentle patting. Beginning one minute after withdrawal, temperature readings were obtained at two minute intervals from the palmar surface of the index finger, the dorsum of the wrist and the flexor surface of the midportion of the forearm of both the cooled and the uncooled upper extremity. In the 10 control subjects and in the 8 patients with dermatomyositis, the temperature response was identical except in the index finger of the immersed extremity. The recovery of the immersed wrist and forearm was seldom complete in twenty to thirty minutes, and usually at the end of this period the temperature was several degrees below the initial temperature. In no instance did the temperature of the chilled wrist and forearm rise above the original temperature. In the unimmersed extremity, the temperature of the index finger fell 1 to 3 degrees C (1.8 to 5.4 degrees F) after immersion of the other extremity, and recovery was complete two to seven minutes after withdrawal of the immersed extremity. This was interpreted as increased vasomotor tone initiated by the cold stimulus. The unimmersed wrist and forearm showed no significant change in temperature.

In the 10 control subjects without vascular disease, the index finger showed the characteristic response to overcooling. The immersed index finger returned to its original temperature at an interval varying from six to sixteen minutes after withdrawal from the bath. Recovery was followed by a rise of the temperature of the index finger from 1 to 4 degrees C (1.8 to 7.2 degrees F) above the original temperature and above that of the nonimmersed index finger. This rise persisted for ten minutes or longer.

In 5 of the cases of dermatomyositis the index finger failed to return to its original temperature or to the temperature of the nonimmersed index finger within twenty to thirty minutes (cases 1, 2, 3, 5 and 7). In 1 instance (case 9) recovery was delayed, however, the characteristic rise

occurred. In 2 instances the response was normal. One of the patients with a normal recovery temperature response had Raynaud phenomena, while 1 of the patients with delayed recovery had no Raynaud phenomena.

The temperature studies on the controls and on the patients with dermatomyositis were made at room temperature varying from 20 to 25 C. During a given study the room temperature did not vary more than 1 degree C. Subsequent studies on 2 normal controls showed that the recovery of the chilled index finger was equally rapid at room temperatures of 20 and 25 C although the initial skin temperature was lower at the cooler room temperature. The recovery period of the patient with diffuse scleroderma and Raynaud phenomena was much slower at 20 than at 25 C. We have also determined the

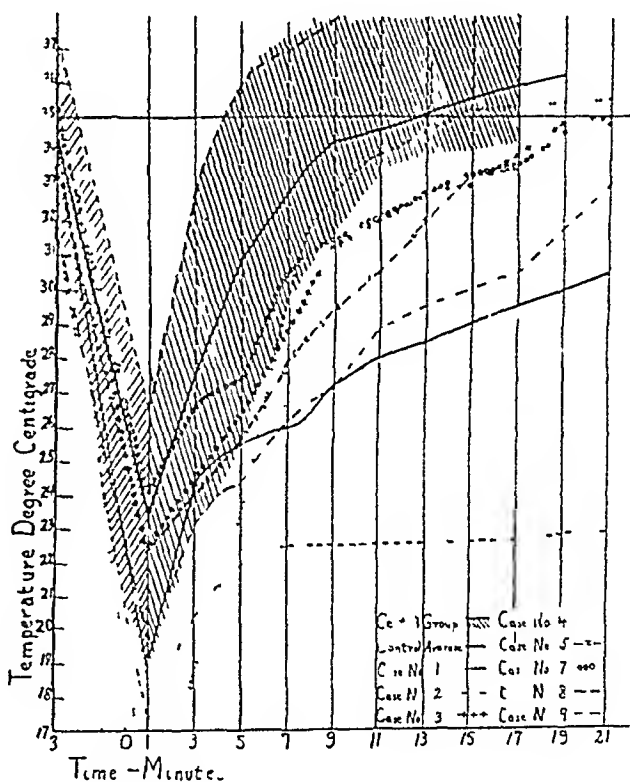


Fig. 4—The temperature recovery response of the index finger after chilling in water at 0 C for three minutes in 10 normal controls (shaded areas indicate range of response) and 7 patients with dermatomyositis.

response to overcooling in 2 patients with obstructive vascular disease of the large arteries of the upper extremities. In both, the recovery of the immersed index finger was delayed and there was no rise above the original temperature or above the temperature of the nonimmersed fingers.

Space does not permit an adequate discussion of the technical difficulties in obtaining reliable readings of skin temperature studies or in

interpreting them<sup>26</sup> To us the observations in our cases of dermatomyositis suggest that there was an impaired flow of blood to the vessels of the skin of the fingers in 5 instances

In 2 instances (cases 1 and 5) the patient's entire body was immersed in water at 20 C for ten minutes. The room temperature was 25 C. In each instance the extremities showed severe cyanosis which persisted for thirty minutes after the bath. The trunk and the proximal portions of the extremities recovered before the distal parts. The temperature of the skin of the fingers did not return to the original level in thirty minutes after the bath. The production of cyanosis at 20 C is in accord with attacks in patients with Raynaud's disease. Lewis<sup>25a</sup> produced typical Raynaud attacks in patients at temperatures of 15 to 20 C. It is interesting that the patient in case 5 gave no history of Raynaud phenomena although objective evidence revealed the condition.

Biopsies of skin were obtained in 4 cases, and sections of muscle were obtained in all except 1 case (case 4). All sections were routine surgical specimens which were fixed in solution of formaldehyde, embedded in paraffin and stained with hematoxylin and eosin. No special stains were employed. The sections showed atrophy of the epidermis and slight perivascular lymphocytic infiltration in the corium. None of these sections was obtained from an area exhibiting a rash. In case 5, in which clinically the patient exhibited diffuse sclerodermatous changes, the corium appeared denser than normal and partially hyalinized. No vascular lesions were observed.

The 8 biopsy specimens of muscle showed considerable histologic variation. In all there were demonstrable abnormalities. Degenerative changes of the muscle fibers, such as vacuolation, loss of striation, hyalinization, variation in staining, fragmentation and atrophy, were observed occasionally, however, we were unable to be certain that many of these changes were not artefacts in our sections. The most constant alteration was an increase in muscle nuclei. Usually the nuclear increase was of the sarcolemma type, that is, of the muscle cells lying beneath the sarcolemma membrane. In many areas there were columns of nuclei which appeared to lie in the central portions of the longitudinally sectioned fibers. These nuclei were elliptic or round and were larger and con-

tained less chromatin substance than usual. Occasionally similar-appearing nuclei were seen in the central portions of transversely sectioned muscle fibers. In a few sections the sarcolemma nuclei showed degenerative changes, such as pyknosis and karyorrhexis. Giant cells occasionally were encountered. These consisted of large numbers of centrally placed nuclei lying in a poorly defined cytoplasmic substance. Phagocytosis of fibers by mononuclear cells was observed frequently. The degree of inflammatory response in the interstitial tissue was variable but usually slight. The cells were predominantly histiocytes and lymphocytes, although plasma cells and polymorphonuclear leukocytes occasionally were encountered. In 2 instances small amounts of brown pigment granules were observed in the interstitial tissue. Perivascular inflammatory cells were present in every section but usually were not numerous. In many sections there was an apparent focal increase in interstitial tissue. The small arteries and arterioles usually appeared normal, although in a few instances there was moderate thickening of the media. No vessel showed proliferative or necrotizing changes or infiltration of the wall with leukocytes.

In an effort to determine the specificity of the histologic changes of dermatomyositis, we examined a number of surgical biopsy specimens from patients with other conditions. This group included 4 sections of normal muscle removed during surgical operations and sections of muscle from 1 patient with torticollis, 2 patients with lupus erythematosus disseminatus, 4 with acute rheumatic fever, 1 with acute glomerulonephritis, 1 with chronic glomerulonephritis, 1 with malignant hypertension, 1 with Volkmann's contracture, 3 with periaarteritis nodosa, 1 with thyrotoxicosis with marked muscular atrophy and 1 with myotonia dystrophica. In many of these sections there were apparent degenerative changes such as atrophy of the fibers, vacuolation of the cytoplasm, loss of striation, fragmentation of the fibers and variation in staining of the fibers. In addition, an apparent slight focal increase in muscle nuclei was encountered frequently.

In the 3 specimens of muscle from patients with periaarteritis nodosa, characteristic vascular lesions were present. In addition, in each instance there were extensive focal increase in muscle nuclei, nuclear degenerative changes, phagocytosis of fibers, interstitial inflammatory changes and focal increase in interstitial connective tissue. In biopsy specimens from 1 of the 2 patients with lupus erythematosus, 1 of the 4 patients with acute rheumatic fever and the

26 Cobet, R. Die Hauttemperatur des Menschen. *Ergebn d. Physiol.* **25** 439-516, 1926. Weatherly, J. H. Skin Temperature Changes Caused by Smoking and Other Sympathomimetic Stimuli, *Am. Heart J.* **24** 17-30 (July) 1942.



patient with myotonia dystrophica, the muscle showed degenerative, proliferative and interstitial changes which were not distinguishable from the changes in our cases of dermatomyositis

There is general agreement that the histologic changes in the skin in dermatomyositis are non-specific The usual alterations are atrophy of the epidermis, edema and perivascular infiltra-

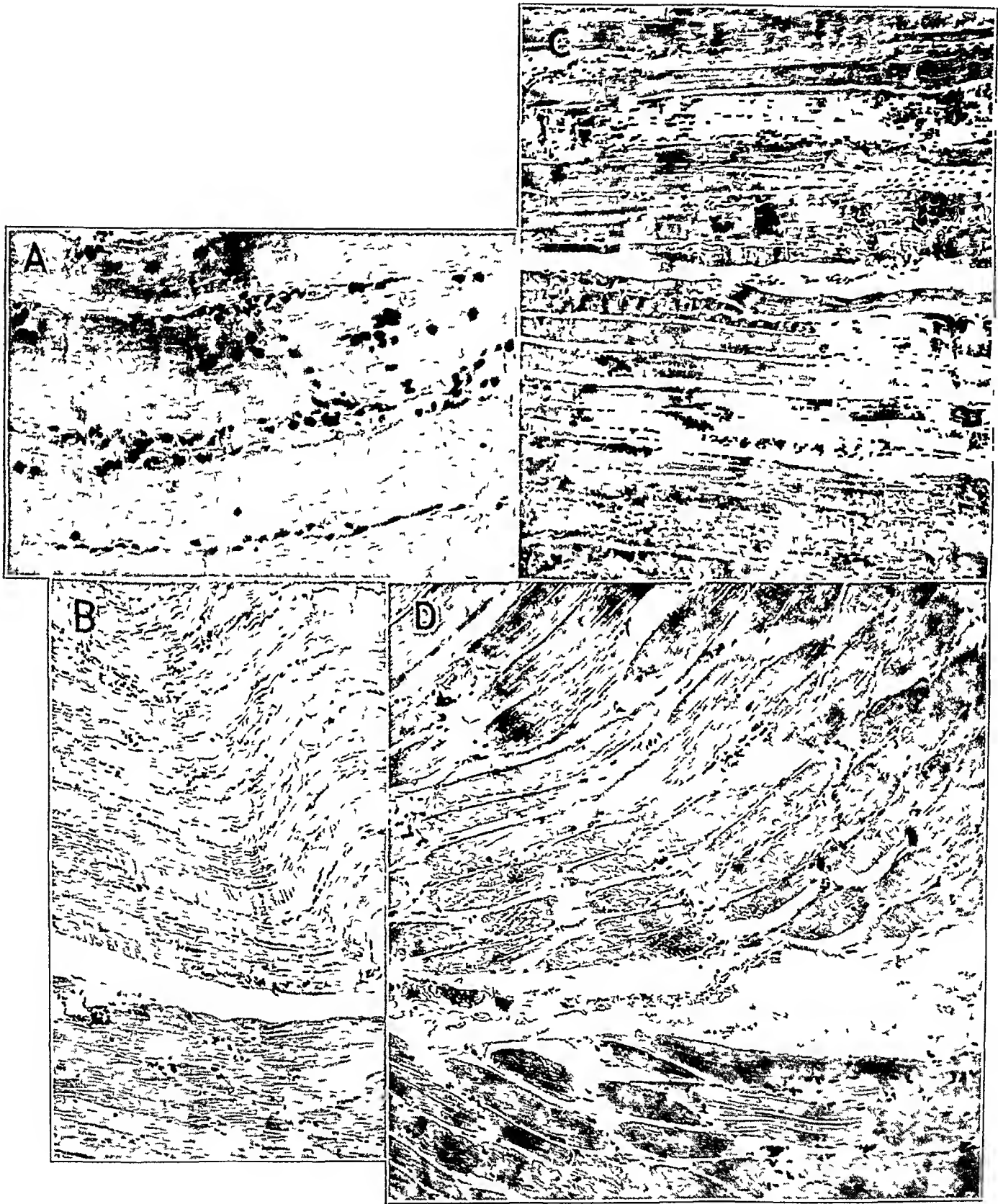


Fig 5—Biopsy specimens of muscle A, from case 1, note the apparent phagocytosis of necrotic muscle fibers B, from case 2, note the nuclear proliferation and the slight interstitial inflammatory reaction C, from a case of disseminated lupus erythematosus, there are extensive proliferation of muscle nuclei and a slight interstitial inflammatory reaction D, from a case of myotonia dystrophica, note the muscle giant cells and the nuclear proliferation

tion of the corium with lymphocytes and plasma cells. The vessels of the corium may be narrowed.

In the muscle similar pathologic changes have been reported by many observers.<sup>27</sup> The degree of involvement is variable. Certain muscles or portions of muscle may not be involved, hence negative results of biopsy do not exclude this diagnosis. This was observed in case 9 of our series, in which the initial biopsy specimen showed no change while a second specimen showed the usual changes. There may be hemorrhage into the muscle. The interstitial connective tissue may be edematous or increased in amount. A variable degree of infiltration with inflammatory cells, mainly lymphocytes, occurs in the interstitial tissue. Occasionally lymphoid follicles ("lymphorrhages")<sup>28</sup> may be present. The arterioles may appear normal. Often they appear dilated. The walls of the vessels may be thickened and may show extensive changes.<sup>28</sup> The muscle fibers show proliferative and degenerative changes. Muscle giant cells may occur and sarcolemma nuclei may be increased. Degenerative changes in the muscles include edema of the fibers, loss of striation, fragmentation, atrophy, necrosis with phagocytosis, and hyaline, granular, fibinous and vacuolar degeneration.

These histologic changes in the muscle are not specific for dermatomyositis. Similar muscle changes in muscles have been observed in many other diseases, such as rheumatoid arthritis,<sup>29</sup> pneumonia,<sup>30</sup> thyrotoxicosis<sup>31</sup> and a variety of other disorders.<sup>27</sup>

27 von Meyenburg, H. Die quergestreifte Muskulatur, in Henke, F., and Lubarsch, O. Handbuch der Speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 9, pt. 1, pp. 299-508. O'Leary and Waisman<sup>1a</sup>. Kinney and Maher<sup>1c</sup>. Keil<sup>1d</sup>. Keller<sup>2a</sup>.

28 Keil<sup>1d</sup>. Keller<sup>2a</sup>.

29 Curtis, A. C., and Pollard, H. M. Felty's Syndrome. Its Several Features, Including Tissue Changes, Compared with Other Forms of Rheumatoid Arthritis, *Ann Int Med* **13** 2265-2284 (June) 1940.

30 Forbus, W. D. Pathologic Changes in Voluntary Muscle. I. Degeneration and Regeneration of the

## SUMMARY

In 9 new cases of dermatomyositis in adults described in this report evidence of involvement of muscles was present in every instance. Frequently there were tenderness, weakness and atrophy of skeletal muscles. Occasionally the so-called vital striated muscles of deglutition and respiration were affected. In all instances biopsy specimens of skeletal muscles revealed certain histologic changes. Evidence is presented to indicate that these microscopic lesions are not specific for this disorder.

Involvement of the skin occurred in 7 of the 9 cases. In 2 instances the mucous membranes of the mouth were affected. In 1 case there was diffuse scleroderma, and in 2 others sclerodermatous changes were confined to the hands. A history of Raynaud phenomena was elicited for 4 patients.

Extensive laboratory studies revealed no constant abnormality other than spontaneous creatinuria. Carbohydrate metabolism, as indicated by several types of tests, was apparently normal. Studies of the reaction to overcooling as shown by the cutaneous temperature gave results typical of Raynaud's syndrome in the 4 patients with a history of this disturbance and in 1 additional patient without such a history.

The variability of the manifestations in this series of cases was sufficient to arouse doubt as to whether "dermatomyositis" is a single clinical entity. A similar view is obtained from reading previous reports of cases of this disorder. In addition to clinical laboratory and pathologic data, it may be necessary to follow the course of the illness for a prolonged period before the diagnosis may be established with certainty.

Dr. Dawson of the Pathology Department of Vanderbilt Hospital, Dr. King of the Physiology Department, Dr. Mason of the Biochemistry Department, and Dr. Youmans of the Department of Medicine, gave suggestions and assistance in this study.

Department of Medicine, Vanderbilt University

Rectus Abdominis in Pneumonia, *Arch Path* **2** 318-339 (Sept.) 1926.

31 Dudgeon, L. S., and Urquhart, A. L. Lymphorrhages in Muscles in Exophthalmic Goitre, *Brain* **49** 182-186 (June) 1926. Freudenthal<sup>2a</sup>.

# STUDIES IN ACUTE MYOCARDIAL INFARCTION

## III DIAGNOSIS AND LOCATION OF THE INFARCT BY ELECTROCARDIOGRAM

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In previous papers<sup>1</sup> we have considered the clinical and laboratory features presented by 378 cases of acute myocardial infarction. The excellent early discussions of the topic<sup>2</sup> so emphasized the clinical aspects that myocardial infarction should be, as Henry Christian described it<sup>3</sup> "an easily diagnosable condition." In the great majority of cases the diagnosis of acute infarction of the myocardium can be made or at least suspected, on clinical evidence alone. However the list of conditions considered in the differential diagnosis of acute infarction is lengthy (Herrick has mentioned 28). We found that but 50 per cent of our patients were admitted with the diagnosis of acute infarction and that in 20 per cent of the cases the admission diagnosis contained no mention of the heart whatsoever.<sup>4a</sup> The electrocardiogram therefore must play a major role in confirming the clinical diagnosis or in revealing the presence of an unsuspected infarction. As part of our study we decided to consider the value and accuracy of the electrocardiogram in the diagnosis of acute myocardial infarction.

### MATERIAL AND SELECTION OF CASES

During the period from Jan 1, 1929 to Dec 31, 1941, 508 patients were discharged from the hospital or died with a final diagnosis of acute myocardial

1 Baer, S, and Frankel, H. Studies in Acute Myocardial Infarction. I. The Clinical Picture, *Ann Int Med* **20** 108 (Jan) 1944, II. Laboratory Procedures as Diagnostic Aids, *ibid* **20** 115 (Jan) 1944.

2 (a) Herrick, J B. Clinical Features of Sudden Obstruction of Coronary Arteries, *J A M A* **59** 2015 (Dec 7) 1912. (b) Levine, S A, and Tranter C L. Infarction of Heart Simulating Acute Surgical Abdominal Conditions, *Am J M Sc* **155** 57 (Jan) 1918. (c) Wearn, J T. Thrombosis of the Coronary Arteries, *ibid* **165** 250 (Feb) 1923. (d) Gardiner, H C. Coronary Arterial Occlusion, *ibid* **168** 181 (Aug) 1924. (e) Christian, H A. Cardiac Infarction. An Easily Diagnosable Condition, *Am Heart J* **1** 129 (Dec) 1925. (f) Hamman, L. Symptoms of Coronary Occlusion, *Bull Johns Hopkins Hosp* **38** 273 (April) 1926.

3 Herrick, J B. On Mistaking Other Diseases for Coronary Thrombosis, *J M Soc New Jersey* **32** 590 (Oct) 1935.

infarction. With the exception of 20 cases that we felt had a typical clinical picture (history, friction rub, etc), no case formed part of this study unless there were diagnostic electrocardiographic or necropsy changes. The use of chest leads was begun at Jewish Hospital shortly after their recommendation by Wolferth and his associates.<sup>5</sup> Every case included on the basis of the electrocardiogram alone was reviewed by the senior author. No electrocardiogram was considered diagnostic unless it presented the changes recommended by Levine, Wolferth and his co-workers<sup>6</sup> and Katz.<sup>7</sup> With these diagnostic criteria, a number of cases of sudden death were eliminated because necropsy was not done. Many cases of old infarction were not included because the electrocardiogram did not exhibit characteristic evidence of a new infarction. There remained for consideration 378 cases.

Electrocardiographic diagnoses were classified under the following headings: (1) anterior infarction, (2) posterior infarction, (3) anteroposterior infarction, (4) infarction present but location uncertain, (5) electrocardiogram not diagnostic and (6) bundle branch block. At necropsy the cases were divided into instances of anterior, of posterior and of anteroposterior infarction.

### THE ELECTROCARDIOGRAPHIC DIAGNOSIS

One must be aware of the possibilities and limitations of electrocardiography. Abnormal electrocardiograms have been obtained for human beings as early as one hour and as late as twenty days after the acute attack. Baines<sup>8</sup> stressed the fact that absence of diagnostic electrocardiographic changes is due to (1) failure to take sufficient tracings, (2) the presence of mul-

4 (a) Wolferth, C C, and Wood, F C. Electrocardiographic Diagnosis of Coronary Occlusion by Chest Leads, *Am J M Sc* **183** 30 (Jan) 1932. (b) Wood, F C, Bellet, S, McMillan, T M, and Wolferth, C C. Electrocardiographic Study of Coronary Occlusion, *Arch Int Med* **52** 752 (Nov) 1933.

5 Levine, S A. *Clinical Heart Disease*, Philadelphia, W B Saunders Company, 1936.

6 Wolferth, C C, and Wood, F C. Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of the Left Ventricle, *Arch Int Med* **56** 77 (July) 1935. Footnote 4.

7 Katz, L N. *Electrocardiography*, Philadelphia, Lea & Febiger, 1941.

8 Baines, A R. Electrocardiogram in Myocardial Infarction, *Arch Int Med* **55** 467 (March) 1935.

multiple fresh infarctions, (3) the presence of bundle branch block, (4) the presence of pericarditis and (5) a critically ill patient. In a series of 34 cases Feil, Cushing and Hardesty<sup>9</sup> found the electrocardiogram diagnostic in 80 per cent.

Electrocardiograms were taken for 321 of our patients (table 1). For all but 18, or 94 per cent, a diagnosis of acute myocardial infarction was made. Of the 18 for whom this was not done, 13 had only one electrocardiogram taken and 5 were given a diagnosis of bundle branch block. We see no reason to disagree with Barnes,<sup>8</sup> who stated that repeated electrocardiograms should reveal the infarction in practically every case.

One of the more controversial topics in this field has been the localization of the acute myocardial infarction. Wood and his associates<sup>4b</sup> found anterior infarction a bit more common than

and Master, Jaffe and Dack<sup>14</sup> reported an almost identical frequency.

The distribution of our cases can be seen in the chart and in tables 1 and 2. There were 201 cases of anterior and 118 of posterior infarction. It would seem that acute myocardial infarction occurs more often in the anterior portion of the

TABLE 2—Distribution of 378 Cases of Acute Infarction

	Recovered	Died	Total
Anterior infarction			
Electrocardiogram only	120	29	149
Electrocardiogram and necropsy		28*	28
Necropsy only		24	24
Total cases			201
Posterior infarction			
Electrocardiogram only	86	15	101
Electrocardiogram and necropsy		5	5
Necropsy only		12	12
Total cases			118
Anteroposterior infarction			
Electrocardiogram only	5	2	7
Electrocardiogram and necropsy		4*	4
Necropsy only		1	1
Total cases			12
Infarction present location uncertain	15	4	19
Electrocardiogram not diagnostic	4	1	5
Bundle branch block		3	3
No electrocardiogram or necropsy		20	20

\* See text

left ventricle. These figures are statistically significant.<sup>15</sup>

This difference becomes even more striking when the cases studied at necropsy are considered (table 3). Of the 74 fatal cases in which autopsy was done, 52, or 70 per cent, were instances of anterior infarction, 23 per cent of posterior and 7 per cent of anteroposterior. These percentage differences are highly significant statistically. The question arises why the incidence of anterior infarction at necropsy was even greater than that found by electrocardiograms alone.

The answer to this is not difficult to obtain. In table 1 it is seen that definite location of the

TABLE 3—Location of Acute Infarction at Necropsy

	74 Cases	Percentage of Total
Anterior	52	70
Posterior	17	23
Anteroposterior	5	7

infarct could not be made by electrocardiogram in 39 of 321 cases (12 per cent). Twenty of the 39 patients died, and autopsy was performed on 12. Of these 12 patients, 11 were found to have anterior infarction and 1 anteroposterior infarction. This is in keeping with the finding of

14 Master, A. M., Jaffe, H. L., and Dack, J. The Treatment and Immediate Prognosis of Coronary Artery Thrombosis, *Am Heart J* 12:549 (Nov.) 1936.  
15 Pearl, R. Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1940.

TABLE 1—Location of Acute Infarction by Electrocardiogram

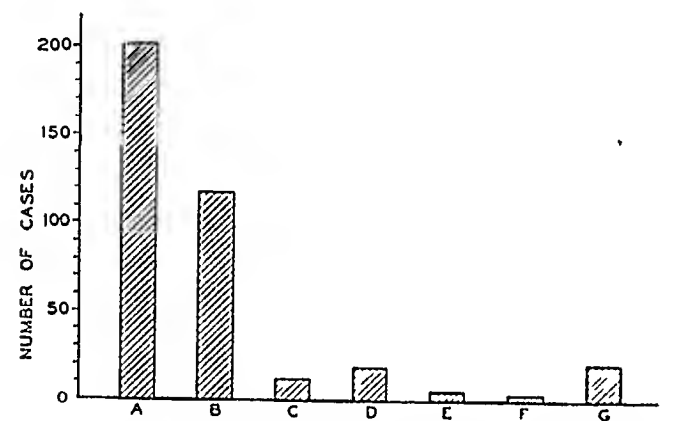
	Cases		Deaths	
	Number	Percentage of Total	Number	Percentage
Anterior	167	52	47	28
Posterior	108	34	22	20
Anteroposterior	7	2	2	28
Acute infarction, location uncertain	21	7	6	28
Electrocardiogram not diagnostic	13	4	9	69
Bundle branch block	5	1	5	100
Totals	321	100	91	28

posterior, and Willius<sup>10</sup> reported anterior infarction in 56.3 per cent of his cases and posterior in 43.7 per cent. Rosenbaum and Levine<sup>11</sup> also found anterior infarction more frequent. In a necropsy study Bean<sup>12</sup> reported that 71 per cent of the infarcts were located in the anterior and apical portions of the left ventricle. In contrast to these figures, Barnes and Ball<sup>13</sup> in unselected autopsy material found little difference in the occurrence of anterior and posterior infarction,

9 Feil, H., Cushing, E. A., and Hardesty, J. T. Accuracy in the Diagnosis of Myocardial Infarction, *Am Heart J* 15:721 (June) 1938.  
10 Willius, F. A. Life Expectancy in Coronary Thrombosis, *J. A. M. A.* 106:189 (May 30) 1936.  
11 Rosenbaum, F. F., and Levine, S. A. Immediate Prognosis of Acute Myocardial Infarction, *Arch Int Med* 68:913 (Nov.) 1941.  
12 Bean, W. B. Infarction of Heart. III. Clinical Course and Morphological Findings, *Ann Int Med* 12:71 (July) 1938.  
13 Barnes, A. R., and Ball, R. G. The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Post Mortem Examinations, *Am J M Sc* 183:215 (Feb.) 1932.

Wood, Bellet, McMillan and Wolfeith,<sup>4b</sup> who stated that most of the infarcts missed by electrocardiograms are anterior

Another factor that would increase the autopsy incidence of anterior as compared with posterior infarction is the greater mortality of anterior myocardial infarction. We plan to consider specifically the factors influencing mortality in a separate paper. It can be seen from table 2, however, that 81 of our 201 patients with anterior infarction (40 per cent) died, as contrasted to 32, or 27 per cent, of the 118 patients with posterior infarction. This difference is of significance statistically. The question of the relative mortality of anterior and posterior myocardial infarction has been controversial. Wood and his associates,<sup>4b</sup> VanderVeer and Brown<sup>16</sup> and Stroud<sup>17</sup> have all expressed the opinion that anterior myocardial infarction is far more serious



Distribution of 378 cases of acute infarction according to location. A, anterior infarction, B, posterior infarction, C, anteroposterior infarction, D, location not certain, E, electrocardiogram not diagnostic (no autopsy), F, bundle branch block (no autopsy), G, diagnosis on clinical evidence (no autopsy)

than posterior. Master and his associates,<sup>14</sup> on the other hand, stated that the prognosis of anterior and that of posterior infarction are about equal, and Willius<sup>10</sup> said that the situation of the infarct has little influence on death or survival. Rosenbaum and Levine<sup>11</sup> agreed with this. It is of course true that a number of factors influence the mortality in the individual case of myocardial infarction. But by and large we feel, as have the observers cited,<sup>18</sup> that a patient with an anterior myocardial infarction has less chance of recovery than one with an infarct on the posterior surface of the left ventricle.

16 VanderVeer, J. B., and Brown, L. E. The Diagnosis and Prognosis of Coronary Occlusion, Pennsylvania M. J. 39: 303 (Feb.) 1936.  
17 Stroud, W. D., in discussion on Levine, S. A., and Levine, H. D. Electrocardiographic Study of Lead IV, with Special Reference to Findings in Angina Pectoris, Tr. A. Am. Physicians 50: 303, 1935.  
18 Wood and others<sup>4b</sup> VanderVeer and Brown<sup>16</sup> Stroud<sup>17</sup>

THE ACCURACY OF THE ELECTROCARDIOGRAM

Another topic considered in this study was the accuracy of the electrocardiogram. Feil, Cushing and Hardesty<sup>9</sup> expressed the opinion that it is accurate in 100 per cent of acute single infarctions. A correlation of our autopsy and electrocardiographic material revealed 16 cases in which the electrocardiogram did not correctly localize the infarct (table 4). These cases were included under their correct category in table 2 (see asterisks).

Of the 16 patients, 8 had but one cardiogram taken before death, 2 had a bundle branch block and 2 were given a diagnosis of acute infarction of uncertain location. Therefore, their cases should not justly be considered as instances of electrocardiographic errors, as Barnes has emphasized.<sup>4</sup> Of the remaining patients, 3 had anteroposterior infarctions that were partially but not completely diagnosed. In just 1 case (interpreted as one of posterior and found to be one of anterior infarction) was there a definite diagnostic error. It seems justifiable to state that the localization of an acute myocardial infarction by the electrocardiogram is a highly accurate procedure.

COMMENT

It is difficult to explain the differences of opinion concerning the incidence and mortality of anterior and of posterior infarction.

The published series of cases of acute infarction have been sufficiently large to eliminate the errors incident to random sampling. The methods of selecting the cases cannot entirely explain these differences. The same observers<sup>19</sup> that reported a greater incidence of anterior infarction found little difference between the mortality of

TABLE 4—Discrepancy Between Electrocardiographic and Autopsy Evidenced in 16 Cases

No. of Cases	Electrocardiographic Diagnosis	Autopsy Diagnosis
7	Myocardial disease (only one tracing taken)	Anterior infarction
2	Bundle branch block	Anterior infarction
2	Acute infarction, location not certain	Anterior infarction
2	Anterior infarction	Anteroposterior infarction
1	Posterior infarction	Anteroposterior infarction
1	Posterior infarction	Anterior infarction
1	Myocardial disease old infarction (only one tracing taken)	Anteroposterior infarction

anterior and that of posterior infarction. Further detailed autopsy studies may help clarify this topic, as would more exact descriptions of the acute attack, of the location of the arterial thrombosis and of the position of the myocardial necrosis. It is noteworthy that our postmortem

19 Willius<sup>10</sup> Rosenbaum and Levine<sup>11</sup>

incidence of anterior infarction is identical to the 71 per cent of anterior and apical infarction found by Bean<sup>12</sup> at autopsy

As far as therapy is concerned, these differences are purely academic. But they are of some importance in helping determine the prognosis of the individual case. Considering our data, we find it difficult to avoid the conclusion that anterior infarctions occur oftener than posterior and are more serious.

#### SUMMARY AND CONCLUSIONS

The diagnosis and location of the infarct were considered in 378 cases of acute myocardial infarction. Electrocardiograms taken in 321 cases revealed the presence of infarction in 94 per cent. On electrocardiographic study alone, 52 per cent

of the infarcts were found to be anterior and 34 per cent posterior. Of 74 patients coming to necropsy, 70 per cent had anterior, 23 per cent posterior and 7 per cent anteroposterior infarction.

Anterior myocardial infarctions are more frequent and more serious than posterior infarctions. Infarction of the anterior wall of the left ventricle is more apt to be missed by electrocardiograms than posterior involvement. Electrocardiographic diagnosis and location of the infarction are highly accurate.

Completion of this study would have been impossible without the assistance and advice of Dr. Harold L. Goldburgh, Dr. A. Margolies and Dr. Joseph C. Doane.

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# LIFE EXPECTANCY AFTER AN ATTACK OF MYOCARDIAL INFARCTION

REPORT OF A CASE OF SURVIVAL FOR NINETEEN YEARS AFTER CORONARY THROMBOSIS

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NEW ORLEANS

Initially myocardial infarction resulting from coronary occlusion was regarded as a rapidly fatal condition. This impression was probably well substantiated by the diagnoses of preelectrocardiographic days, seldom made except in cases of the most severe form. This attitude persists despite the numerous more optimistic prognosticators, perhaps it is best that all clinicians have a wholesome respect for this serious disease and that therefore they be more than ordinarily cautious in its treatment. On the other hand, one must realize the virtue of presenting a favorable life expectancy to the patient recovering from myocardial infarction. Herrick<sup>1</sup> was the first (1912) to lend a gleam of hope to the situation by assuming the possibility of a long period of survival after recovery.

Electrocardiography clarified the diagnostic difficulty, the development of the method was rapid, and its accuracy has been proved, so that statistical evaluation of the life expectancy after recovery from myocardial infarction is now possible. With the advent of the electrocardiographic method, reports of five year survivals appeared in the literature. Then Burton and his associates<sup>2</sup> reported a case of the condition verified by necropsy in which the patient survived seven years. Jegorow<sup>3</sup> presented a case of multiple infarction verified post mortem in a man whose initial attack occurred fifteen years before. Conner and Holt<sup>4</sup> claimed to have seen a case in which the patient survived seventeen years, but they lack pathologic confirmation. White,<sup>5</sup> in 1933, reported his case of the disease,

confirmed by autopsy, in which the patient survived for seventeen and a half years, and, in 1936, he claimed a new record of survival for twenty-four years<sup>6</sup> after an attack of coronary thrombosis.

With the general acceptance of such notable work, one hesitates to question White's reliability as a chronologist. However, in reviewing his two reports, we find a weakness nonexistent in our study. His 2 patients were assumed to have the initial attack of coronary occlusion on the basis of the history alone and in the course of their years of survival had other such episodes, but there were no electrocardiographic studies. We feel justified in reporting the present case, for a search of the literature shows that it is the first instance of myocardial infarction due to coronary thrombosis in which there was electrocardiographic confirmation at the onset and in which the patient lived for so long a time, nineteen years and thirty days from the initial occlusion until his death, from thrombosis, both the initial and the terminal attack being confirmed by autopsy.

## REPORT OF CASE

*History*—R. J. S., an attorney who was known to have hypertension, experienced a typical attack of coronary occlusion in February 1924, at the age of 42. The diagnosis was confirmed by progressive electrocardiographic changes and was concurred in by the attending physician, Dr. Sidney K. Simon, and by two cardiologic consultants, Dr. B. R. Heninger and Dr. J. B. Elhott.

An acceptable regimen was adhered to, with six weeks' rest in bed and eight months' abstinence from work. Adjusting himself well to his disability, the patient resumed partial activity and gradually returned to his legal practice on a restricted basis. For nineteen years he was under close medical observation. He experienced frequent episodes of anginoid pain, which were relieved by use of analgesics and of drugs to dilate the coronary vessels. On several occasions he had severe, prolonged transthoracic pain, with mild circulatory collapse, but never had a frank episode of congestive heart failure. Numerous electrocardiographic studies were made, the only significant change after the initial series being a progressive shift from a normal deflection to a pro-

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1 Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* **59** 2015 (Dec. 7) 1912.

2 Burton, J. A. G., Cowan, J., Kay, J. H., Marshall, A. J., Rennie, J. K., Ramage, J. H., and Teacher, J. H. Fibrosis of the Myocardium with Electrocardiographic and Postmortem Examinations, *Quart. J. Med.* **23** 293, 1930.

3 Jegorow, B. Die intravitale Diagnose des Myokardinfarktes, *Ztschr. f. klin. Med.* **106** 71, 1927.

4 Conner, L. A., and Holt, E. The Subsequent Course and Prognosis in Coronary Thrombosis, *Am. Heart J.* **5** 705, 1930.

5 White, P. D. Longevity After Coronary Thrombosis, *J. A. M. A.* **100** 233 (Jan. 28) 1933.

6 White, P. D. A New Record in Longevity After Coronary Thrombosis, *J. A. M. A.* **108** 1796 (May 22) 1937.



nounced left axis deviation. The roentgenographic silhouette did not change in either the anteroposterior or the lateral projection, and the measurements remained within normal limits.

He lent himself well to medical interest and was seen by numerous prominent internists, all of whom concurred in the diagnosis of myocardial infarction due to coronary occlusion.

In July 1924 Dr Emanuel Libman, who saw the patient in consultation, agreed to the diagnosis of myocardial infarction and suggested the possibility of ven-

reading of the blood pressure was 70 systolic and 30 diastolic (previous average reading 185 systolic and 90 diastolic). Oxygenation and sedation, infusion of a concentrated solution of dextrose and limited, but adequate, administration of fluids were the initial therapeutic measures. Twenty-four hours later he experienced pain on the right side of the thorax and hemoptysis (considered indicative of pulmonary infarction). The patient recovered from the immediate shock and did well for four days, then anuria developed and was successfully combated with various measures, including

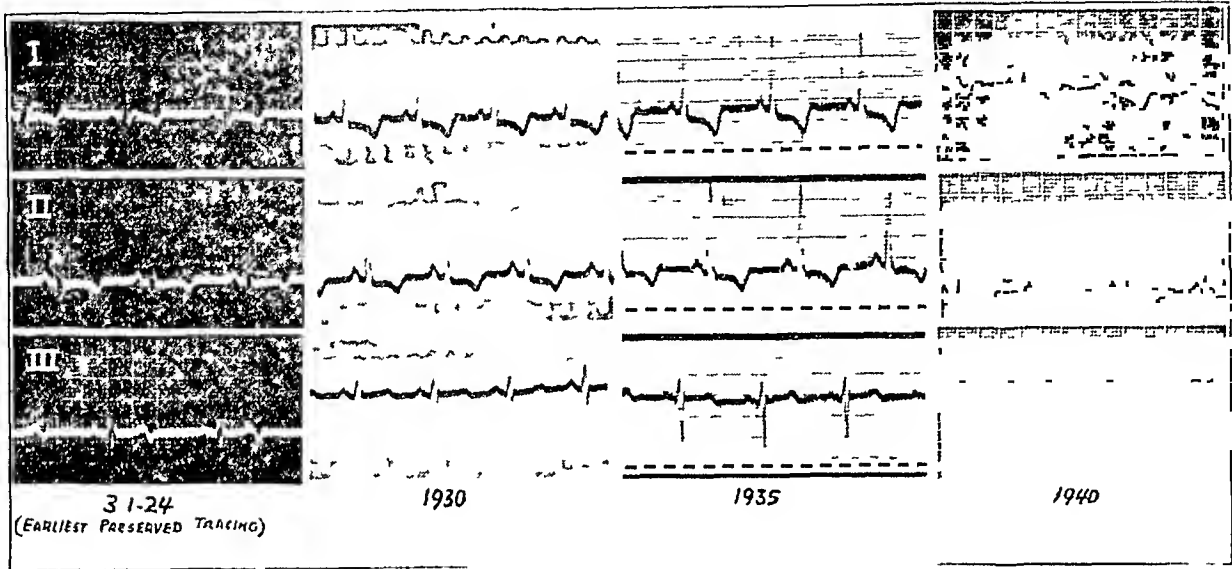


Fig 1—Electrocardiograms taken at intervals during the period of survival after myocardial infarction (1924-1943)

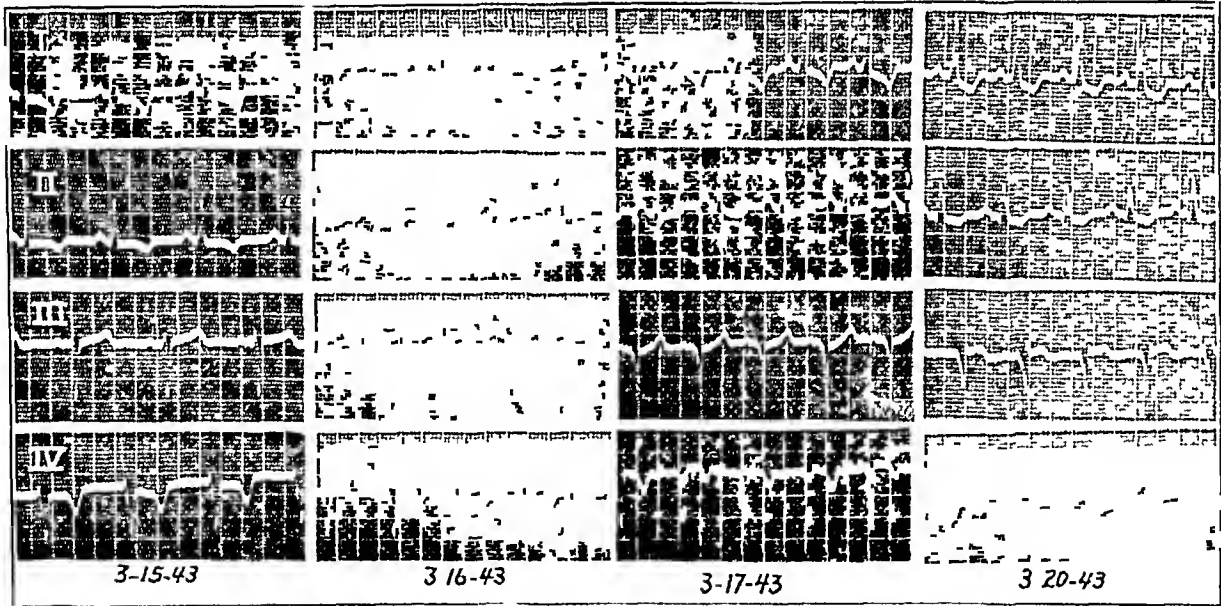


Fig 2—Electrocardiographic tracings taken during the terminal illness with coronary thrombosis. The patient died March 30, 1943.

tricular aneurysm but added "There is not enough evidence for a definite diagnosis of secondary aneurysm of the heart." Drs. Hubert Schoonmaker, Franz Groedel, John Musser and W. W. Hamburger all made confirmatory reports.

On three occasions it was necessary to give the patient a large dose of sulfathiazole—once for nasofacial cellulitis, resulting from nasal furunculosis, and twice for severe prostatitis. He withstood this medication well.

Throughout the years he was a prominent, active, successful attorney and teacher.

On March 15, 1943, while in court, he experienced a typical attack of coronary thrombosis. The earliest

administration of plasma. The sequence of events was congestive heart failure, which enforced digitalization, and terminal peripheral vascular collapse, with death on the fifteenth day after the onset of the attack.

*Autopsy*—The heart was enlarged, weighing 575 Gm. There were moderate hypertrophy and dilatation of the left ventricle, absence of any valvular lesion and two definite areas of scarring on the left ventricle, indicative of old, well healed infarcts. The anterior descending branch of the left coronary artery was occluded 3 cm from its origin, resulting in an area of infarction, measuring approximately 3 by 2 cm, in the antero-inferior portion of the intraventricular septum, as well

as an area in the adjacent anterior wall of the left ventricle, 2 cm in diameter

Microscopic study revealed definite signs of old myocardial scarring, as well as the evidence of recent infarction

The other observations at necropsy were merely incidental. There was no ventricular aneurysm. The lungs showed only areas of atelectasis, most of the alveoli were filled with so-called heart failure cells.

#### COMMENT AND CONCLUSION

We shall not review the literature or compile a statistical report. Master, Dack and Jaffe<sup>7</sup>

<sup>7</sup> Master, A. M., Dack, S., and Jaffe, H. L. Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, *Arch Int Med* 64:767 (Oct) 1939

adequately performed this task in 1939, when they published a study of 500 cases of coronary occlusion from Mount Sinai Hospital, with a bibliography covering 2,803 clinical reports and 1,241 necropsy studies.

We have not attempted to compute an average period of survival for myocardial infarction, but we hope by reporting this interesting case to lend credence to White's contention that survival and physical activity are possible years after an attack of acute coronary occlusion and that the prognosis for all victims should be considered from this optimistic point of view.

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# PALINDROMIC RHEUMATISM

A "NEW," OFT RECURRING DISEASE OF JOINTS (ARTHRITIS, PERIARTHRITIS, PARAARTHRITIS) APPARENTLY PRODUCING NO ARTICULAR RESIDUES—  
REPORT OF THIRTYFOUR CASES, ITS RELATION TO "ANGIO  
NEURAL ARTHROSIS," "ALLERGIC RHEUMATISM" AND  
RHEUMATOID ARTHRITIS

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We wish to describe an unusual, oft recurring disease of joints and adjacent tissues, 34 cases of which have been studied in the arthritis service of the Mayo Clinic since 1928. Its outstanding features are multiple afebrile attacks of acute arthritis and periartthritis, and sometimes also of para-arthritis, with pain, swelling, redness and disability generally of only one, but sometimes of more than one, small or large joint, in an adult of either sex. The attacks appear suddenly and develop rapidly. They generally last only a few hours or days and then disappear completely, but they recur repeatedly at short or long, *irregularly* spaced intervals. Despite the frequent recurrences and the transitory presence (in some cases at least) of an acute or subacute inflammatory polymorphonuclear exudate in the articular tissues and cavity, little or no constitutional reaction or abnormality is revealed by laboratory tests, and no significant functional, pathologic or roentgenographic residues occur even after years of disease and scores of attacks.

The disease has not been described in any of the many new and old textbooks on articular conditions which we have examined. In certain ways it resembles, and in other ways it differs from, conditions described in 1911 and 1913 by Solis-Cohen<sup>1</sup> and in 1939 by Kahlmeter.<sup>2</sup> The

resemblances of our cases to, and their differences from, those of Solis-Cohen and of Kahlmeter will be noted hereafter.

## ILLUSTRATIVE CASES

Six typical cases are described in detail. Data on the remaining 28 cases and on these 6 cases are presented in table 1 and summarized in the text.

CASE 1 (table 1)—*First recognized case of palindromic rheumatism in this series*

A woman aged 21 came to the Mayo Clinic Aug 2, 1928, complaining of "arthritis" of eight years' duration. Her first attack was at the age of 13 years (August 1920), nine months before her first menses. Suddenly both big toes and a knee became swollen, red and painful. The attack lasted about a week, then the joints recovered completely. A month later she began to have a series of attacks which successively involved any one of several joints almost continuously during 1920 and 1921. The great toe and metacarpophalangeal joints usually were affected. Generally only a single joint was affected at one time and then only for twelve to thirty-six hours. There would be, for example, much swelling and "vicious pain" in a joint in the morning, then suddenly in the afternoon that joint would become completely well, without even residual tenderness, until its reinvolvement a few days later, but some other joint would be affected meanwhile. Attacks occurred in some joint or other almost daily, when the feet were affected she often had to stay off them because of severe pain. With attacks appearing or subsiding almost daily, she estimated that she had several hundreds of them during 1920 and 1921, and yet after each attack the affected joint became "completely well every time." Then the disease changed its pace, and the pattern of attacks altered notably.

During 1922 and 1923 the patient had only four or five attacks or small "groups of attacks" yearly. One joint of a toe or finger would be affected for two or three days, pain was severe enough to keep her awake and limit her activities temporarily. Then she would

2 Kahlmeter, G. Y a-t-il des formes de rhumatisme articulaire et periarticulaire d'une nature reellement allergique? *Acta med Scandinav* 102 432-443, 1939.

\* Division of Medicine, Mayo Clinic

Presidential address presented by Dr. Hench at a meeting of the American Rheumatism Association in New York, June 10, 1940, also presented at a meeting of the Central Society for Clinical Research in Chicago, Nov 8, 1941.

1 Solis-Cohen, S. Certain Angioneurotic Manifestations in and Around Joints, Frequently Mistaken for Gout and Rheumatism, *Tr. Coll. Physicians, Philadelphia* 33 309-311, 1911, On Some Angioneural Arthroses (Periarthroses, Pararthroses) Commonly Mistaken for Gout or Rheumatism, *Tr. A. Am. Physicians* 28 739-757, 1913. *Am. J. M. Sc.* 147 228-243 (Feb) 1914.

be well for three or four days, until another joint was affected, generally less severely and only for two days. At intervals of about one week she would have a third and a fourth attack lasting only a half or one day. After such a small group or chain of three or four bouts her joints were entirely well for two or three months. Diagnoses of rheumatism, fallen arches and arthritis were made. Treatment included tonsillectomy, physical therapy and shoe correction. In 1924 and 1925 she had only one short run of attacks yearly. During them she could not wear shoes or play the piano. She had no attacks in 1926, but in 1927 the attacks became more extensive and more severe. The fingers, left wrist, shoulders, left knee, ankles and toes were affected. Four or five joints would swell and become painful, tender and stiff for from one to four days, then the process would subside quickly without residual disability. Attacks occurred in October and December of 1927 and in May and twice in July of 1928.

In the four years before the onset of articular symptoms (1916 to 1920) short attacks of hives, which were thought to be due to strawberries and fish, appeared five or six times yearly and involved the eyes, face, ears, abdomen, arms or legs. The hives appeared only occasionally near joints, they generally were located elsewhere. During 1920 and 1921, when her joints were more or less continually affected, she had only three or four attacks of hives lasting one or two days and promptly controlled by epinephrine. Between 1924 and 1926, when articular attacks were least frequent, she had the most severe attacks of hives, lasting three or four days and coming four or five times yearly. Although the hives rarely were present when joints were affected, if an articular attack was already in progress the subsequent appearance of hives seemed to aggravate the joints. The joints also were made worse by heat and by menses, but not by changes in weather. The patient and her father, a physician, considered that the hives and the arthritis, since the two conditions rarely occurred coincidentally, were not related or were related only remotely.

The patient's history otherwise and the family history were not significant. She did not have any other allergic manifestations (such as migraine, asthma or hay fever) and had not lost weight despite her illnesses.

**Physical Examination**—The physical examination on the patient's admission to the clinic gave essentially negative results except for certain joints. There were swelling and tenderness at the proximal interphalangeal joint of the right third finger, the left knee, which had just recovered from an attack, was normal, the right ankle was slightly swollen, tender and painful on motion, the right fourth toe was definitely swollen, tender and painful. There was no urticaria. The next day several metacarpophalangeal joints were red and a small patch of urticaria was present on the abdomen. No focal infection was discovered.

**Laboratory Data**—The urine was normal. The hemoglobin reading was 75 per cent (Dare method), and erythrocytes numbered 4,500,000 and leukocytes 9,400 per cubic millimeter of blood. The flocculation test for syphilis gave negative results. The concentration of uric acid (whole blood) was 4 mg per hundred cubic centimeters, of calcium (serum) 10.2 mg and of potassium (serum) 4.4 mg. The sedimentation rate was not estimated in 1928.

**Roentgenograms**—Those of the hands and of the right foot showed a normal condition.

**Preliminary Diagnosis**—This was recurrent acute arthritis of unknown origin or questionable allergic arthritis. Diagnoses of rheumatoid (chronic infectious,

atrophic) arthritis or of recurrent rheumatic fever could not be made because of the absence of residual articular or cardiac pathologic changes after "hundreds" of attacks. Despite the occurrence of repeated short attacks with complete remissions and the involvement of the great toes, a diagnosis of gout was not seriously entertained, gout rarely affects females, especially young females, and tophi or definite hyperuricemia was not present. Furthermore, the clinical pattern of the disease in this case differed materially from that of gout, in that the attacks lasted a shorter time and came much more frequently. Nevertheless, it was decided to note the effects of high and low purine diets and of colchicum.

**Subsequent Course**—The patient was given a diet rich in purines, the blood uric acid rose from 4 to 4.3 and 4.7 mg per hundred cubic centimeters, instead of becoming worse during this time, the involvement of the joints rapidly cleared up. However, a severe attack of hives occurred and lasted three days. In the next few days two or three other attacks of hives were provoked, apparently by sweetbreads but also by other foods. Cutaneous tests with a wide variety of foods, including fish, sweetbreads and strawberries, gave negative results. During the attacks of urticaria the joints remained normal. The urticaria was relieved by epinephrine and colloid baths, but it was neither relieved nor prevented by the use of colchicum. The patient was dismissed with advice to avoid the foods suspected of causing the urticaria. This she did for four months. A month after dismissal she had pain in the joint of one big toe for a few hours, but no urticaria.

Some months later, after she had eaten clams, lobsters and shrimps, a short attack of hives but no arthritis developed. We saw the patient again in 1932, the value for blood uric acid was 3.4 (normal 2 to 4.5) mg per hundred cubic centimeters. Since 1929 she has taken a normal diet. She has had no further attacks of arthritis. Between 1929 and 1940 she had about six attacks of urticaria. She thought they were due to eating strawberries and fish, but she often had eaten these foods without subsequent hives. The patient now lives in Rochester and has been under repeated observation. Her joints and heart are still entirely normal (February 1942).

**Comment on Case 1**—The relationship between the patient's attacks of hives and the arthritis is obscure. The two diseases rarely coincided, but because of the urticaria we suspected, though we could not prove, that the articular reactions also might represent an allergic response. The significance of the fact that the arthritis disappeared when the patient adopted certain dietary restrictions is counterbalanced by the fact that the arthritis did not later reappear after the patient returned to a general diet. A diagnosis of "allergic arthritis," therefore, was considered unproved but allowed to stand for purposes of indexing and further study.

**CASE 16 (table 1)**—*The case of most severe involvement in this series, with arthritis, para-arthritis, peri-arthritis*

This case will be reported in considerable detail, as the involvement was the most severe and the case exhibits best the features of the disease and is illustrated

with several photographs (figs 1 to 10) which show clearly the transient, yet recurrent nature of the attacks.

A housewife aged 39 was admitted to the clinic Dec 11, 1936 because of (1) recurrent "rheumatism," with painful swellings of joints almost daily for six years, (2) subcutaneous para-articular swellings, generally near but not over joints, occurring frequently for four years, and (3) small intracutaneous or subcutaneous nodules, appearing frequently at various sites of pressure and elsewhere for three years.

"*Rheumatism*."—In April 1930 the patient began to have recurrent attacks of swelling, pain, redness and stiffness of various joints, attacks came almost daily, generally lasted only eight to twelve hours, occasionally twenty-four hours, and left the affected site or sites normal until their next involvement. They were so numerous that an almost continuous succession of daily attacks involved some joint or other. While on a summer vacation in 1936 she had, for no known

and proximal interphalangeal joints, a knee or an ankle was affected almost daily. The elbows, shoulders, spinal column, wrists and toes shared in the attacks only about once a week, terminal phalangeal joints were involved two or three times monthly and the hips less frequently. Of all regions affected the shoulders became the most painful, but joints of the fingers swelled the most frequently. Often a finger swelled to twice its normal size and the skin became tight. The recurrent swellings of fingers had been so notable for three years that the skin had been stretched and as the swelling subsided it left the skin markedly wrinkled (fig 1 *a*). When joints were swollen, articular tenderness was pronounced and there was a "deep ache" as though the pain were in the bone. Often joints were sufficiently disabled and painful to force the patient to lie down all afternoon, although she rarely had to undress and go to bed. The more housework she had to do the worse the attacks were, rest moderated but

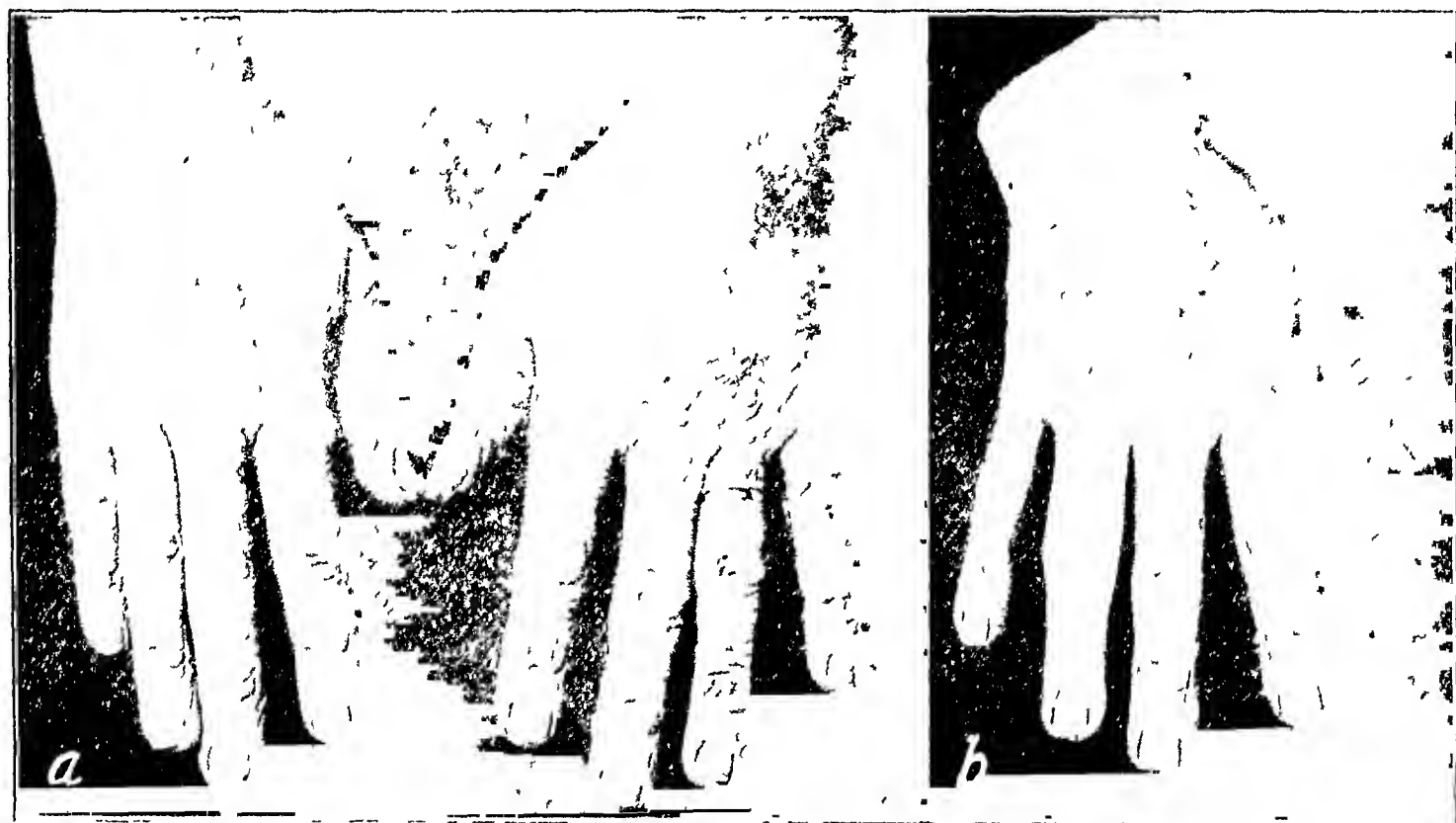


Fig 1 (case 16)—(a) Dec 11, 1936, both hands. The skin over the fingers has been stretched by the recurrent swellings. When the swellings subsided, the skin was left markedly wrinkled. Nodules may be seen (1) on the mesial aspect of the right index finger, (2) over the proximal phalanx of the left fifth finger, and (3) over the terminal joint of the left third finger. The dorsum of the left hand is slightly swollen. (b) Dec 16, 1936, right hand. The proximal interphalangeal joint of the fourth finger is now swollen.

reason been free of daily attacks for a few days, the only time in six years.

Attacks affected one joint or several joints at a time. Usually the patient was well each day until about noon or early afternoon. Then a joint or joints became swollen, painful and often red. The attack reached its maximal intensity usually about 4 or 5 p. m., receded during the evening and disappeared during the night. With few variations such attacks had occurred day after day for six years, yet the joints each morning were generally entirely normal and no deformity or chronic disability had appeared. Joints involved in the order of frequency were those of the fingers, knees, ankles, elbows, toes, shoulders, spine, wrists and hips. When the shoulders, spinal column and hips were affected there was aching pain but no swelling. Other joints definitely swelled. Some metacarpophalangeal

never entirely prevented the attacks. They were worse the week before, and less severe the week after menses. They were not related to weather, season or any known food. The patient did not have asthma, hay fever, eczema or known sensitivity to any drug or food but occasionally she had mild headaches. The articular swellings had been unaffected by numerous treatments, various pills, a diet poor in meat and salt, physical therapy, chiropractic treatments and removal of teeth and tonsils.

*Subcutaneous Swellings (Para-Arthritis).*—During the four years before the patient's admission many of the articular attacks had been accompanied by rather small subcutaneous swellings which lasted one to four days and affected tissues above or lateral to a joint, about a millimeter, on the dorsum of a foot, on the extensor surface of an arm just distal to an elbow

or proximal to a wrist, or over the dorsum of a hand just proximal to one or two metacarpophalangeal joints. Occasionally also one or more finger tips or finger pads (flexor surfaces of the distal phalanges) would swell up in connection with swelling of a proximal interphalangeal or terminal phalangeal joint. These regions of puffiness varied in diameter from that of a dime to that of a silver dollar ( $\frac{7}{10}$  to  $1\frac{1}{2}$  inches, 18 to 40 mm), pitted slightly on pressure, were slightly tender and ached or burned. The finger pads especially would become sensitive for a few hours.

*Intracutaneous or Subcutaneous Nodules*—The patient had also noted for three years the occasional appearance

trauma and appeared especially at sites of pressure. A bump would not precipitate one, but a few hours' pressure of an elbow on the arm of a chair or of the head on the back of a chair or of the buttocks on a chair seat would cause one to form. Hence the patient had padded the arms, seats and backs of her chairs. Such nodules appeared near the elbows frequently, on the back of the scalp two or three times a month and on the forehead occasionally.

*History*—The patient had scarlet fever in 1911, underwent cholecystostomy for obstructive jaundice in 1923, and suffered from pleurisy, pneumonia and phlebitis of one leg and had tonsillectomy performed in 1933. The family history was irrelevant except that one sister had hay fever, another had migraine and two nephews had hives after eating certain foods.

*Physical Examination*—The patient's first examination at the clinic was in the morning, at which time the joints all appeared normal, none were tender or sore. There was slight puffiness, however, over the dorsum of the left hand (fig 1a). Nine small, firm intracutaneous nodules, one near each olecranon process, and seven scattered over the ventral and dorsal surfaces of the fingers were present (figs 1a, 3a and 5). These were elevated about 1 to 2 mm and were about 3 to 8 mm in diameter. The skin of the fingers was wrinkled, and the subcutaneous tissues of the surfaces of the fingers were loose and seemed atrophic, as if there had been much previous subcutaneous swelling (fig 1a). General and neurologic examinations otherwise gave negative results.

*Laboratory Tests*—A flocculation test for syphilis gave a negative result. Many urinalyses were made, all showing a normal picture. Concentrations of uric acid were in whole blood 3.1, per hundred cubic centimeters, in plasma 4.4 mg and in serum 5.0 mg. The value for plasma cholesterol was 175 mg per hundred cubic centimeters, for lecithin 223 mg, for fatty acids 280 mg and for total lipids 455 mg. The sedimentation rate was 10 mm (one hour) before an articular attack and 12 mm (one hour) during an attack. The hemoglobin reading was 14.5 Gm per hundred cubic centimeters, erythrocytes numbered 4,300,000 per cubic millimeter of blood and leukocytes 8,400 to 10,000. Several differential leukocyte counts revealed neutrophils 48 to 68 per cent, lymphocytes 25 to 45 per cent, monocytes 1 to 7 per cent, eosinophils 1 to 5 per cent, filamented cells 38 to 56 per cent and nonfilamented cells 8 to 22 per cent. The sedimentation rates and total and differential cell counts did not vary significantly before, during and after an attack of arthritis.

Roentgenograms of the hands (fig 6), wrists, elbows, knees, ankles, feet and chest were entirely normal. Hemolytic streptococci were readily found in each of three nasopharyngeal cultures. Specific lesions were not produced when they were injected into two rabbits, the animals' joints remained normal. These streptococci when injected into the patient's skin produced only slight reactions. Cutaneous tests with a number of pollens, foods and hairs all gave negative results. The cold allergy test of Horton, Brown and Roth<sup>3</sup> was negative.

*Subsequent Observations*—The patient was studied in the hospital for twenty-seven days (Dec 15, 1936 to Jan 10, 1937). During this time we observed a series

3 Horton, B. T., Brown, G. E., and Roth, G. M. Hypersensitiveness to Cold with Local and Systemic Manifestations of a Histamine-Like Character. Its Amenability to Treatment, *J. A. M. A.* **107**: 1263-1268 (Oct 17) 1936.



Fig 2 (case 16)—Dec 23, 1936 (a) The proximal interphalangeal joint of the right fourth finger is no longer swollen, the terminal joints of the fourth and fifth fingers are now swollen. (b) Swelling on the flexor surface of the left forearm, proximal to the wrist.

of small subcutaneous or intracutaneous nodules or papules near the elbows, knees or wrists and especially on the fingers. They came rather suddenly, lasted sometimes only a few days, but usually about two to five weeks, and then disappeared completely. The only nodule which had persisted had been on the mesial aspect of the right index finger for about one year (fig 5). These nodules were usually somewhat tender, more so than the regions of para-articular puffiness. The nodules seemed to bear a relationship to



of short, acute attacks of arthritis and the appearance on several occasions of swellings of para-articular soft tissues and on four occasions of nodules (fig 1 *b* and figs 2 to 5) At no time was fever present

*Arthritis*—During the twenty-seven days the patient had fifteen attacks of arthritis, chiefly in joints of fingers In nine attacks only joints of fingers (one or more) were affected, and in five, joints other than of fingers In only one were joints of fingers and other

phalangeal joints (not finger pads) Other regions involved during these twenty-seven days were the left ankle twice, the left great toe (whole toe) twice and the left knee, left hip, right shoulder and back once each The same joint was rarely affected on two successive days, generally three or more days elapsed before a given joint was involved again

The patient's joints generally appeared normal each morning Usually an attack began between noon and

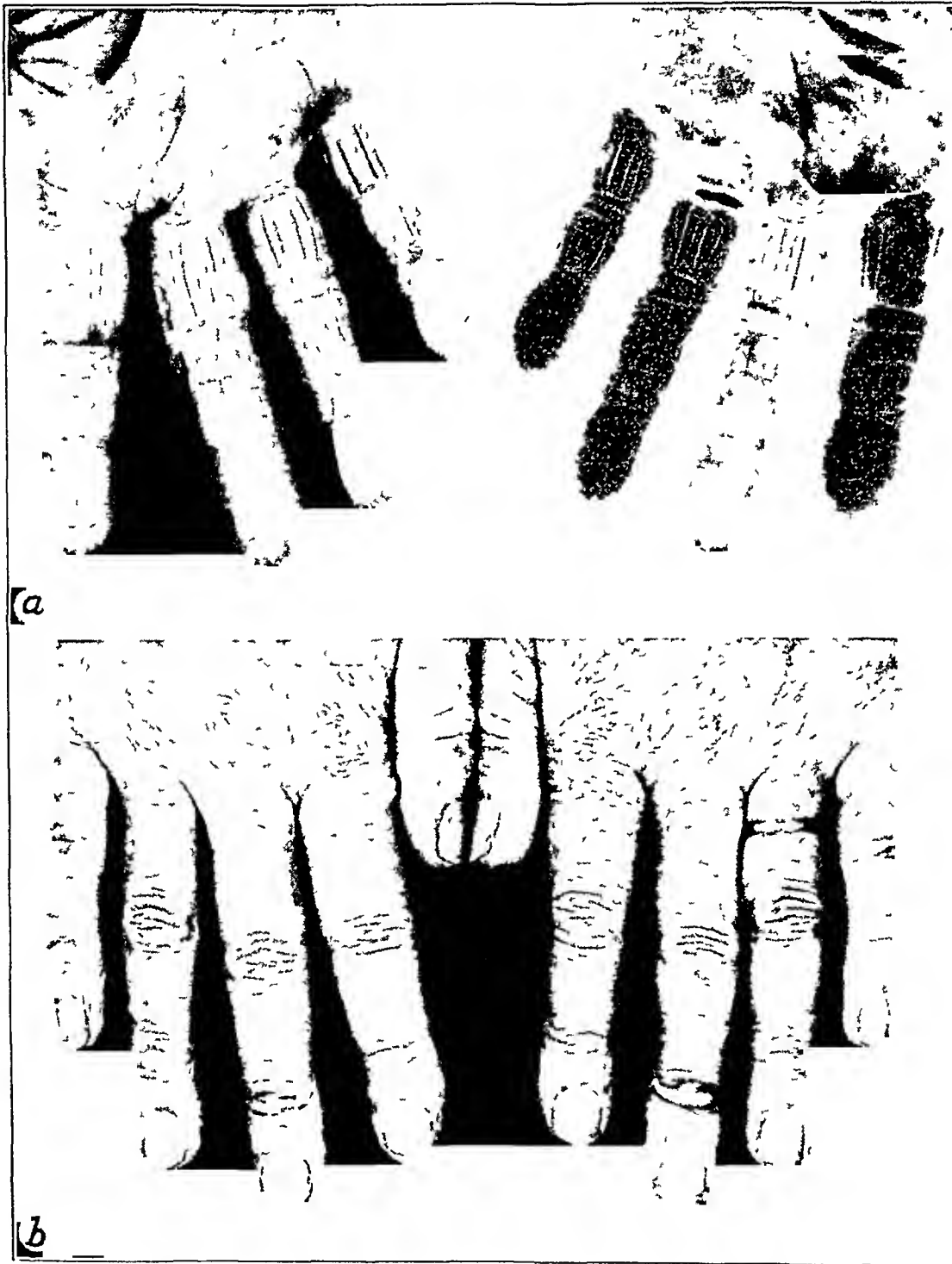


Fig 3 (case 16)—Dec 28, 1936 (a) The pads of the right second and third and of the left third, fourth and fifth fingers are swollen, note the scattered small subcutaneous nodules (b) The terminal joints of the right fourth and fifth fingers are no longer swollen, compare with figure 2 *a*

joints simultaneously attacked In six of the ten attacks affecting joints of fingers only one joint was affected, in three attacks two and in one attack, three. Proximal interphalangeal joints were affected much oftener than other joints of the hands (fig 7) The attack of Dec 23, 1936 involved no proximal interphalangeal joint but affected a metacarpophalangeal joint and was the only attack which involved terminal

3 p m, reached its maximal intensity of swelling and pain in about four or five hours and was practically gone the next morning On the morning after the attack there was generally no objective or subjective evidence of the previous day's attack except occasionally slight tenderness on firm pressure or a faint residual puffiness at the site of the last attack Repeatedly within about twenty-four to thirty-six hours the joints



were fully restored to normal function and also, as the photographs (figs 1 to 4) show, to normal appearance. The amounts of articular swelling present before 4 p. m. were apparent to the naked eye and to the palpating finger but were often not such as could be readily reproduced in photographs. That amount of swelling usually did not appear until between 5 and 9 p. m. On rare occasions an attack began between 9 and 11 a. m. or after the evening meal.

Articular swellings were generally of grade 2 on a grading basis of 1 to 4, rarely less and occasionally more. For example, during one attack the circumference of the proximal interphalangeal joint of the right fourth finger increased from 5.7 to 7.2 cm. and that of the same joint on the right index finger from 6.5 to 7.2 cm. Pain was definite and annoying, generally graded 2 (moderate or notable but not severe). Tenderness of grade 2 was usually present. Redness of grade 1 to 2 and stiffness of grade 1+ to 2.

intercellular and intracellular edema in the epidermis but no other noteworthy changes.

*Para-articular Swellings (Para-Arthritis)*—These occurred on each of fourteen days while the patient was in the hospital, their diameters (0.7 to 1.2 inches, 1.8 to 3 cm.) varied from the size of a dime to that of a 50 cent piece. They affected various parts of the hands oftener than other sites. They appeared on the hands alone on six days, on the hands and elsewhere on six, and elsewhere but not on the hands on two. A favorite site was the dorsum of the right hand proximal to, rather than over, the metacarpophalangeal joints. As indicated in figure 7, three such regions on the two hands were repeatedly affected, but even when the same site was affected on two successive days there was an interval when the swellings disappeared for a few hours. These regions of swelling pitted slightly, were slightly reddened, were tender and ached or burned. Especially notable were the swellings which involved



Fig. 4 (case 16)—Jan. 6, 1937. The terminal joints of the right fourth and fifth fingers are still normal, the proximal interphalangeal joints of the left second and third fingers are swollen and cannot be fully extended.

On twelve of the twenty-seven days there were no attacks of arthritis, possibly as the result of treatment which will be discussed later.

On Jan. 7, 1937, biopsy of the skin, articular capsule and surrounding tissues at the proximal interphalangeal joint of the left index finger was performed during an attack in this joint that had begun about twenty to twenty-four hours before.

When the subcutaneous tissues were exposed some milky fluid ran out, and when the joint was opened cheesy bits of coagulated material came out. The histologic reactions were those of a nonspecific acute inflammation. The coagulated exudate within the joint consisted of a loose fibrin network, enmeshing innumerable leukocytes, mainly polymorphonuclears, in other words, it was a fibrinopurulent exudate (fig. 8). The synovial membrane revealed acute inflammation with widespread exudation of polymorphonuclear leukocytes and notable inflammatory thickening of synovial villi (fig. 9a and b). Eosinophils were not present in significant numbers. No urate crystals were found in sections stained by Galantha's silver stain. Sections of the skin overlying the joint showed the presence of

several finger pads on December 28 again on December 29 and on January 8 (fig. 3a). The pads ballooned out so that the skin over them was taut. The pads were only slightly reddened but were tender, they burned and throbbled and then skin temperatures (with the Constantin and copper galvanometer) were 4 to 6 C (72 to 108 F) higher than those of adjacent unaffected finger pads. The swellings extended up to and occasionally proximal to the skin crease of the corresponding terminal phalangeal joint but the joints themselves seemed to be uninvolved although somewhat stiffened by the adjacent swelling.

Other sites of these para-articular swellings were the flexor and extensor surfaces just proximal to the wrists (fig. 2b), the flexor surface of the metacarpophalangeal joint of the left third finger, the arms just below the olecranon processes, the lateral aspect of the right knee, above the left patella, about the left external malleolus and over the dorsum of either foot. Often these various swellings on the hands and elsewhere though distinct, were not gross enough to show in photographs except as a slight blurring of tissues or

smoothing out of contours and wrinkles, but some of our photographs show them more clearly

**Nodules**—The sites of the nine intracutaneous nodules present on the patient's admission have been mentioned. During the twenty-seven days of observation four new nodules were noted, two on the dorsum of the right wrist, one in the occipital region and one over the



Fig 5 (case 16)—Jan 6, 1937. The nodule visible on the right index finger has been present for a year. The nodule on the thumb has been present for a few hours.

proximal interphalangeal joint of the right thumb, which was visible only a few days (fig 5). The older nodules were for the most part essentially painless, but several of them became sore during one of the articular attacks. One of the original nodules (left index finger) was incised for biopsy December 11. Microscopic examination revealed a nonspecific inflammatory reaction resembling that in the articular capsule but less acute (fig 10 *a* and *b*). The cellular elements of the fibrous tissue were proliferating actively, there were occasional mitotic figures among the young fibroblasts. The tissue was vascular, and occasional polymorphonuclear leukocytes, lymphocytes and plasma cells were present about the small blood vessels. In many of the blood vessels the endothelial cells were tall and swollen.

**Treatment**—During the early stages of the attack of Dec 22, 1936, involving finger joints, subcutaneous injections of 1:1,000 solution of epinephrine hydrochloride, 10 and 8 minims (0.6 and 0.48 cc), given thirty minutes apart, failed to modify the usual progress of the attack. The administration of ephedrine, 7 capsules daily (each  $\frac{1}{8}$  gram, 0.024 Gm) on December 24 and 25, did not apparently influence the attacks. Amphetamine sulfate, 20 mg twice a day, was given December 26 and 27. On December 26 the left great

toe swelled and soft tissue swellings appeared in several other regions, but on December 27 the patient was entirely free of arthritis or swellings, her first "well" day in six months. Intravenous injections of triple typhoid vaccine (25,000,000 and 50,000,000 bacilli) were given December 29 and 31, with satisfactory general reactions, and on January 1 daily injections of histamine for desensitization were begun. From December 27 to January 3 inclusive the patient's joints were free from attacks, although para-articular swellings had occurred December 28 and 29. No articular attacks occurred January 5, 8 and 9, although para-articular swellings occurred January 8 and 9. Whether this unusual freedom from articular attacks was due to the reactions to typhoid vaccine remains problematic. After dismissal the patient was asked to submit again to reactions to typhoid vaccine, but has relied on injections of histamine at home.

On January 8, after para-articular swellings had affected several finger pads and the dorsum of the right hand, 5 cc of a 1 per cent solution of procaine hydrochloride was injected into the sixth, seventh and eighth cervicodorsal nerves on the right side. Within five minutes Horner's syndrome was produced on the right side. Thereafter the cutaneous temperature of the right forearm and hand increased, with an apparent reduction in the pain and burning, and probably also some reduction in the size of the swellings.

The factor of rest seemed to be important. The patient insisted that her attacks in the hospital, despite their frequency, were not as severe as those she had while working at home. Therefore, on several days we prescribed three or four hours of rather strenuous occupational therapy and three or four miles of walking, on these days her attacks were somewhat more severe. Because of this rest factor we are unwilling to make any final conclusions as to the value of the treatments used in the hospital.

The patient was dismissed to continue further treatment at her home: injections of histamine, oral adminis-



Fig 6 (case 16)—Dec 19, 1936. The roentgenogram of the hands (taken after removal of biopsy specimen from the left index finger) is normal despite the fact that the patient has experienced hundreds of episodes of arthritis during the preceding six years.

tration of histaminase and injections of an autogenous hemolytic streptococcus vaccine. She obtained no relief from further use of amphetamine or histaminase. Injections of histamine were given through April 1937; the patient's physician was of the opinion that the injections



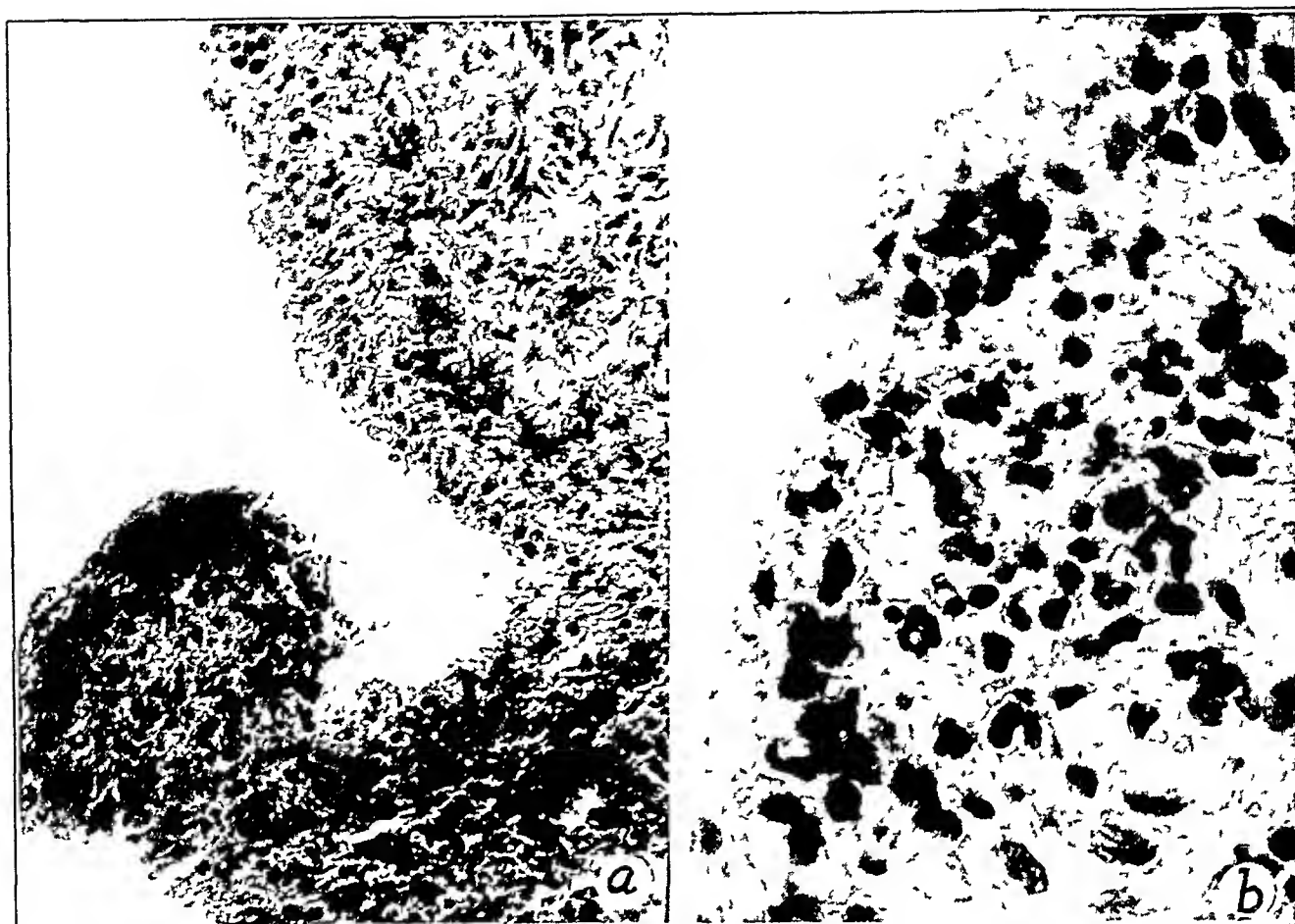


Fig 9 (case 16) —Acute inflammatory reaction present in the synovial membrane during an acute attack. There is widespread exudation of polymorphonuclear leukocytes and notable thickening of the synovial villi (a,  $\times 310$ , b,  $\times 700$ )

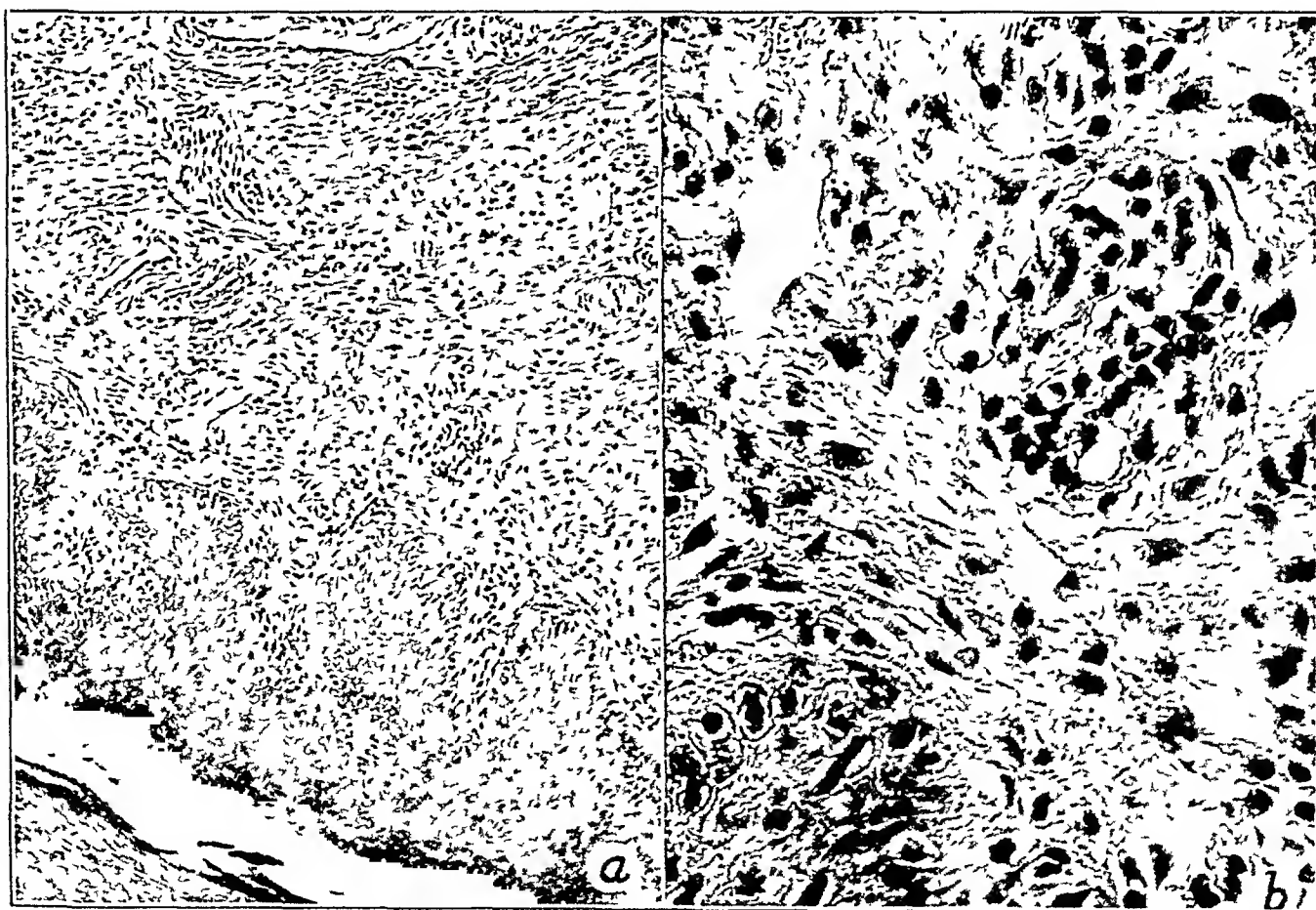


Fig 10 (case 16) —The nonspecific chronic inflammatory reaction present in a subcutaneous nodule. The fibroblasts are proliferating, the tissue is vascular, and occasional inflammatory cells are seen about small vessels (a,  $\times 100$ , b,  $\times 400$ )

longed use of a diet which contained none of the supposedly offending foods had given him no relief, nor had injections of epinephrine. Somewhere along the line a diagnosis of gout had been suggested, but as a physician he thought so little of this diagnosis that he never instituted the appropriate regimen.

In addition to the articular reactions, the patient had had numerous episodes of brawny swelling and induration of each forearm but nowhere else. The affected region became firm and tender for a few days. For two years he had had some precordial pain on exertion. His past history included scarlet fever when he was a child, tonsillectomy in 1920 and influenza.

**Physical Examination**—This gave essentially negative results. Objectively all joints were normal, and roentgenograms of an elbow, knee and wrist revealed nothing significant. Other roentgenograms showed slight hypertrophic arthritis of the thumb and the right hip. This was considered to be the coincidental osteoarthritis usual in a man of his age and entirely unrelated to his chief articular disease. No infected foci were found.

**Laboratory Data**—The patient had mild anemia, the concentration of hemoglobin was 12.9 Gm per hundred cubic centimeters of blood, erythrocytes numbered 4,010,000 per cubic millimeter of blood. Total and differential leukocyte counts and values for blood calcium, phosphatase and cholesterol esters were normal. The value for uric acid in the blood was 4.8 mg per hundred cubic centimeters, that for serum phosphorus 2.6 mg (slightly low) and that for plasma cholesterol 303 mg (slightly high). The sedimentation rate was 54 mm per hour during the swelling on the arm noted hereafter. Culture of material from the nasopharynx revealed green-producing streptococci, which when injected intravenously into rabbits produced hemorrhagic lesions in muscles and periarticular fascia and a hemorrhagic turbid exudate in certain joints. Most of the cutaneous tests made with various foods, including that with chicken, gave negative results. Reactions were slightly positive to whole wheat, beef, cocoa, coffee and tea. While in Rochester the patient ate a duck dinner, forty-eight hours later a painless, colorless, non-tender swelling developed over the left forearm near the wrist but disappeared entirely in a few hours. Joints were not affected.

**Diagnosis**—As in case 1, a tentative diagnosis of 'allergic arthritis' was made, on Feb 4, 1938, largely for indexing purposes, a diagnosis of coronary sclerosis was also made. The patient was dismissed to note the effect of ephedrine, histamine and histaminase, and to keep a food diary.

**Subsequent Course**—Two weeks later, before any treatment had been begun, the patient noted transient swelling of a metacarpophalangeal joint which lasted two days. On March 5, 1938, he wrote that he had had no further trouble. "I don't know when I have been so long without an attack before." He began to take injections of an autogenous streptococcus vaccine, but on Aug 11, 1938 he died of coronary disease.

**Comment on Case 20**—In this, as in the previous cases, a diagnosis of rheumatoid (chronic infectious, atrophic) arthritis or gout seemed untenable. The history and clinical findings suggested the presence of articular reactions of an allergic nature, but this could not be proved nor could the antigen be definitely identified.

The nasopharyngeal streptococci may or may not have been significant. The reason for the patient's apparent improvement after dismissal was not obvious, as the improvement, that is, a respite from attacks, started before the prescribed treatment was begun.

**CASE 27 (table 1)**—*Case in which articular biopsy was made as an attack subsided*

A housewife aged 41 years came to the clinic Jan 23, 1939, because of recurring attacks of arthritis for two years. She had had about 100 attacks in all, each one lasted a few hours or a few days and then disappeared. During the first year the attacks generally lasted less than a week. A year previously several joints of both hands suddenly swelled and were as 'sore as a boil' for two weeks. She could not do housework but did not have fever. Then the hands promptly returned to normal. The longest attack was three weeks, and some of her most painful attacks lasted only a few hours. Sometimes she had two or three attacks a week and sometimes none for three weeks, the average was about one week.

In an attack generally only one joint was affected, a finger joint, wrist, elbow, shoulder, knee or toe, occasionally several joints were involved, but 90 per cent of her attacks affected some part of a hand. Attacks came suddenly at any hour, but more often between 3 and 6 p. m. or in the middle of the night. One hour she would be "feeling grand", the next hour she would be miserable. Swelling and pain reached their maximum within two or three hours. An affected joint became slightly red and sufficiently swollen to iron out wrinkles in the skin and make it shiny. Mild attacks consisted of articular pain without swelling. The pain was throbbing or knife-like, was equally severe day and night and often kept her awake. Disability was such that if a knee was involved she had to go to bed, an affected hand prevented housework.

The patient knew of no cause for the attacks. Attacks were unrelated to work or menses but were less severe in summer. Despite her hundred attacks she had not lost weight and her appetite was good. There was no personal or family history of allergic reactions. The patient had seen several physicians, no definite diagnosis had been made. Tonsillectomy had not stopped the attacks.

**Physical Examination**—On admission the patient was in an attack (fig 11). The proximal interphalangeal joint of the left second (index) finger was swollen and slightly stiff. All other joints appeared normal. The finger remained affected for several days. The only infected focus found was a tooth.

**Laboratory Data**—The sedimentation rate was 8 mm in one hour. The concentration of uric acid was 2.7 mg per hundred cubic centimeters of blood, of cholesterol 315 mg, of cholesterol esters 277 mg, of lecithin 260 mg, of fatty acids 569 mg and of total lipids 884 mg per hundred cubic centimeters of plasma. That of hemoglobin was 13.5 Gm per hundred cubic centimeters of blood. Total and differential leukocyte counts were normal, 2 to 3 per cent of the leukocytes were eosinophils and 17.5 per cent nonfilamented cells. A flocculation test for syphilis gave negative results. Roentgenograms of the hands, elbows and knees and the right foot were normal. An agglutination test for *Brucella abortus* and the cold allergy test gave negative



results Cutaneous reactions to tests with many antigens were all negative except for a reaction of grade 2 to corn and to cocoa

*Subsequent Course*—On February 6 the proximal interphalangeal joint of the left index finger was incised for biopsy, the attack in that joint was subsiding The joint contained an increased amount of normal-looking fluid, and its capsule was thickened Cultures of material from the joint and of the fluid on brain broth and brain agar revealed no organisms

Microscopic examination of tissue from the capsule (fig 12 *a* and *b*) revealed actively proliferating fibrous tissue with many young fibroblasts, a few inflammatory cells, including polymorphonuclear leukocytes, were scattered about small vessels

The patient was fed large amounts of foods which she suspected might be causing the attacks corn, cocoa, macaroni, potatoes, rice, and so forth No attack was precipitated, and on Feb 9, 1939 she felt fine, there was no pain anywhere and she stated that she "could run a race today"



Fig 11 (case 27)—The proximal interphalangeal joint of the left index finger is slightly swollen and stiff This cleared completely in a few days

Histamine desensitization was begun During the patient's stay at the clinic no other attack developed She was dismissed Feb 13, 1939 with instructions to continue the histamine therapy and to have the infected tooth removed These measures did not give permanent relief and she still suffers from the recurrent attacks However, she has not lost weight and does not have articular residues

*CASE 30 (table 1)—Case in which biopsy of wrist was made during an acute attack*

A farmer aged 35 came to the clinic June 22, 1939, because of many attacks of "rheumatism" over a period of six years In 1933 his knees became painful for several weeks, then the pain disappeared About eight months later he began to have recurring short attacks of acute arthritis, and he has had about one hundred and fifty attacks in the past five years Between attacks his joints become entirely normal The attacks appeared any time of day or night, but especially at night, often around midnight He estimated that he had had seventy-five attacks in the hands, twenty-five or thirty in a

shoulder, fifteen each in an elbow or ankle and about fifteen more attacks involving a knee, a hip or the neck The large toe joints were never affected, nor had the patient ever had olecranon bursitis or renal colic Usually only one joint was affected in an attack, occasionally three joints were involved successively, one being attacked as another joint cleared up

A joint began to ache and in about six or eight hours became painful, swollen, red and tender Pain was so severe that for the next one or two days he could not work or sleep At night the severe pain forced him to get out of bed and walk about or use hot or cold applications to get relief During an attack he could not eat with an affected hand, could not dress or shave, and so forth, but had to carry the part in a sling The swelling, pain and redness usually remained for two or three days and then slowly "disappeared 100 per cent, leaving the joint as good as ever" The shortest attack lasted one day, the longest, one week He had never been aware of any fever with the attacks They bore no apparent relation to season, weather or food The patient thought they were sometimes precipitated by overwork and by getting his feet cold and wet There was no family or personal history of allergic reactions

*Physical Examination*—This gave essentially negative results The joints were entirely normal No infected foci were found

*Laboratory Data*—A flocculation test for syphilis gave negative results Roentgenograms of the elbows, knees, hands and wrists were normal The hemoglobin value and the total and differential leukocyte counts were essentially normal 1 and 15 per cent eosinophils and 6 per cent nonfilamented cells The sedimentation rate was 25 mm in one hour The concentration of uric acid (aerobic technic) in whole blood was 3.9 mg per hundred cubic centimeters and in serum 5.2 mg of serum calcium 9.5 mg and of serum phosphorus 3.1 mg, of plasma cholesterol 219 mg, of cholesterol esters 144 mg, of lecithin 203 mg, of fatty acids 379 mg and of total fats 598 mg Many intracutaneous tests made with various antigens gave negative results, cutaneous reactions to whole wheat, oats, corn, rice and cocoa were slightly positive

*Subsequent Course*—At each of five meals the patient had generous amounts of cocoa and whole wheat bread, no attack was produced Between July 5 and 9, 1939, he ate corn and rice at each meal On the afternoon of July 9 his left wrist began to throb and ache That night and the next morning it was slightly swollen, tender and stiff The wrist was incised The tendon sheaths of the extensor muscles of the thumb and of the extensor carpi radialis muscle were found to be filled with a murky-looking fluid In view of the tendonitis, the wrist joint was not opened Cultures of fluid on brain broth and blood agar remained sterile Histologic examination of sections from the tendovaginal sheaths revealed nonspecific inflammation Lymphocytes and a few polymorphonuclears were present about the small vessels and scattered throughout the fibrous fatty tissue (fig 13)

*Treatment*—Histamine desensitization was begun, and the patient was dismissed July 19, 1939, to continue treatment at home

*Follow-Up Study*—In September 1939 the patient wrote that he felt 50 per cent better, he thought perhaps this was due to the injections of histamine He was still having repeated attacks in various joints, but they were not so severe He had been unable to connect his attacks with any food eaten In April 1940 the patient was still having painful attacks in the hips, knees or wrists with severe swelling, which lasted generally three

or four days, occasionally a week. He had had about six attacks since dismissal from the clinic, between attacks the joints still became normal.

*Comment on Case 30*—Although we may have precipitated an attack by giving the patient corn and rice, the patient's subsequent observations on food indicate that this was a spontaneous, not an induced, attack. The character and pattern of attacks also suggested that allergic reactions of some sort were repeatedly affecting articular and periarticular (tendinous) tissues, but we were unable to prove that the condition was allergic. Results with histamine were equivocal.

interphalangeal joint of a finger, fifteen or more in the left knee, eight to ten in the right knee and in a metacarpophalangeal joint, five or six in a terminal phalangeal joint of a finger and three in the left wrist. The feet had been affected on only one occasion, when, after playing golf once his heel hurt so that he had to walk on the toes of that foot for a day. There was no swelling. It is possible that this single attack in a foot was not similar to the attacks elsewhere.

The attacks usually started in the afternoon. First the joint became sore, then within a few hours it became swollen, red and tender. Usually a painful red region the size of a dime (1 to 2 cm) appeared near the joint. The joint ached and throbbed, pain and disability were notable but not sufficient to require narcotics or to put the patient to bed. If a knee was affected he limped, if a finger was involved, he could

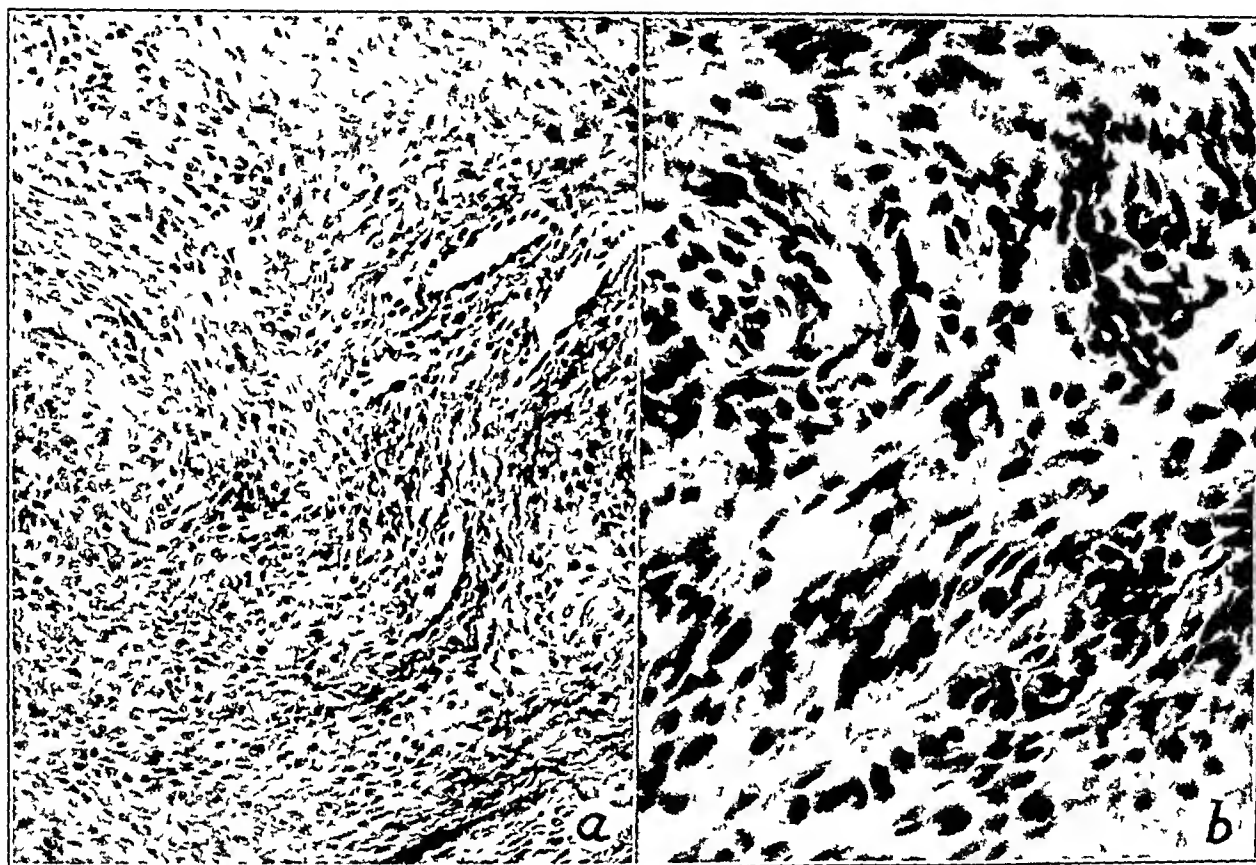


Fig 12 (case 27)—Character of the inflammatory reaction present in the tissues from the capsule of the swollen joint illustrated in figure 11. Fibroblasts are proliferating actively. A few inflammatory cells, including polymorphonuclear leukocytes, are scattered about small vessels. This attack was subsiding clinically at the time the biopsy specimen was taken. (a,  $\times 170$ , b,  $\times 700$ )

*CASE 34 (table 1)—Case in which articular biopsy was made between attacks*

A man 33 years of age came to the clinic Nov 21, 1939, because of recurrent "joint pains" for ten years. In 1929 the proximal interphalangeal joint of the right third finger suddenly swelled and became red and tender. Having played baseball that day, he attributed the swelling to possible trauma, although he recalled no specific injury. The joint recovered entirely in two days, but every one or two months since then he had had a short attack of acute arthritis involving certain joints, but only one joint at a time. The attacks usually lasted twenty-four to forty-eight hours and then disappeared entirely. As a rule he has had six to eight attacks yearly, but in 1935 he had twenty attacks. He estimated that he had had from eighty to a hundred attacks within ten years, about fifty in a proximal

not type. The length of the attack varied, the shortest, in a finger, lasted twelve hours, the longest, in a knee, lasted four or five days. The time between attacks generally was four to eight weeks, occasionally four months, and on certain occasions the patient had had a short chain of two (never more) consecutive attacks, a metacarpophalangeal joint being affected one day and a midphalangeal joint the next day.

On Oct 20, 1929, a month before his admission, the patient struck his left knee lightly against a knob in his automobile, the next day he noted a small red sore spot at the left knee near the head of the fibula, the knee became swollen, warm, red, tender and painful for two days, for a few hours thereafter it was less painful and the patient drove a car 300 miles (482 kilometers). This made the knee sore again for a few hours. The attack rapidly disappeared, and the knee



recovered fully within twenty-four hours. Ten days before admission the patient's left wrist became stiff and sore, a small, firm, freely movable nodule appeared "just beneath the skin" but disappeared within six days. Ten or twelve times a red sore spot, "the size of a dime," has appeared on the palm of either hand, unaccompanied by swelling, it remained sore for a few

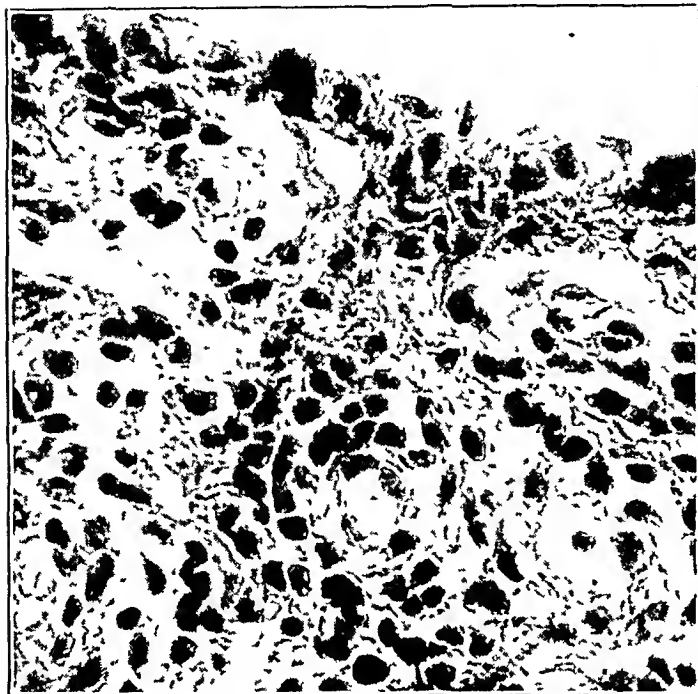


Fig 13 (case 30)—Histologic appearance of tissue from an inflamed tendovaginal sheath. Nonspecific inflammation with lymphocytes and a few polymorphonuclear leukocytes is present about blood vessels and scattered through the fibrous fatty tissue ( $\times 600$ )

hours and then disappeared. They seemed to bear no time relationship to the articular attacks. On six or eight occasions a finger tip became sore and red for twenty-four to thirty-six hours.

Throughout the patient's illness no constitutional reaction, fever, anemia or loss of weight had been noted, and despite the scores of attacks the joints regained their normal appearance and full function.

Precipitating factors appeared to be slight trauma on the occasions noted and possibly foods, the patient suspected that onions and potato salad might have precipitated attacks, but attacks had persisted when he avoided these foods. Numerous cutaneous tests with foods had all given negative results. There was no personal or familial evidence of allergy, hay fever, asthma, hives or migraine. Season and weather did not influence the attacks. Most of the attacks appeared without obvious cause.

Past treatment had included alveolectomies, tonsillectomy, hot applications and various medicines, without relief. The joints had been too painful to permit massage. In August 1938 the patient took 350 grains (22 Gm) of sulfanilamide within five or six days, but the next attack came after the usual interval.

*Physical Examination*—On the patient's admission physical examination gave essentially negative results. The appearance and function of the joints were normal, and no cardiac lesion or focal infection was found.

*Laboratory Data*—A flocculation test for syphilis gave negative results. The urine, hemoglobin content and total blood cell and differential counts (eosinophils 2 per cent) were normal. The concentration of uric acid (aerobic technic) was 4.3 mg per hundred cubic centi-

meters in whole blood and 5.4 mg in serum. The concentration of serum calcium was 10.1 mg per hundred cubic centimeters, of serum phosphorus, 2.7 mg, of plasma cholesterol, 252 mg, of cholesterol esters, 174 mg, of lecithin, 238 mg, of fatty acids, 312 mg, and of total lipids, 564 mg. The sedimentation rate on Nov 22, 1939 was 6 mm in one hour, on November 30, during a mild attack, 30 mm. Cutaneous tests with a large number of foods, pollens and other antigens and the cold allergy test all gave negative results except for a cutaneous reaction of grade 2 to salmon.

*Subsequent Course*—We attempted to provoke an attack by the use, on separate occasions, of 0.8 mg of histamine, given subcutaneously, 50,000,000 typhoid bacilli, given intravenously, and ergotamine tartrate, 0.5 cc given twice on one day and 1 cc twice on the next day, but no attack occurred. On Nov 26 and 27, 1939 the patient received a general diet plus large amounts of onions, potatoes and potato salad. No attack occurred on these days. On November 28 a spot (2 by 2 cm in diameter) over the left thenar eminence was red and slightly sore, and the internal malleolus of the right ankle became slightly tender and slightly red. These changes lasted for seventy-two hours. They were not aggravated by a subcutaneous injection of histamine. The patient then was given a diet rich in purines and fats for five days. No attack was provoked by this or by two meals rich in salmon. The uric acid content was 3.4 mg per hundred cubic centimeters of blood before the high purine diet and 3.9 mg after five days of the diet.

On Nov 24, 1939, during a remission of the disease, the left knee was incised for biopsy, a piece of synovial membrane and muscle being removed. The joint cavity, cartilages and so forth were carefully inspected grossly and appeared entirely normal. Histologic examination revealed the synovial tissue and muscle to be normal (fig 14), despite the fact that there had been at least fifteen attacks in this knee. Cultures of the removed



Fig 14 (case 34)—Normal synovial tissue from the knee. The biopsy specimen was obtained during a remission after at least fifteen attacks in this knee ( $\times 150$ )

pieces of synovial membrane and muscle on brain broth were negative.

*Follow-Up Study*—The patient was dismissed Dec 18, 1939, to be under the care of his physician at home. We suggested that a food diary be kept and that the effects of ephedrine, ergotamine, histamine desensitization, histaminase, typhoid vaccine, Rosenow's arthro-

tropic streptococcus vaccine and antigout therapy be investigated further. In a letter of April 1940, the patient wrote that he had had no treatment since dismissal and had had three mild attacks. Each had lasted six to twenty-four hours, the joints then recovered completely.

#### ANALYSIS OF CLINICAL MATERIAL

Data on the frequency, duration and outcome of the acute attacks in all 34 cases encountered in eleven years (1928 to 1939) are presented in table 1.

*Relative Incidence of the Disease*—After case 1 was noted by one of us (P. S. H.) in 1928, the disease was not seen (or recognized) until 1931 and 1932, when 5 and 3 cases respectively were observed. None were encountered between 1933 and 1935, but since 1936 from 3 to 9 typical cases have been observed yearly. The relative incidence of this disease according to its present rate of recognition at the Mayo Clinic is, therefore, about 5 or 6 cases in about 4,000 to 4,500 cases of "rheumatism" (articular and muscular diseases of all types) observed yearly by the clinic's consultants on diseases of joints. Thus the condition seems rather rare, but the rate of recognition will probably increase somewhat.<sup>4</sup>

*Sex Incidence*—The incidence was relatively equal in each sex (15 males to 19 females), this is a striking contrast to the sex incidence either of rheumatoid arthritis (among patients with which females preponderate) or of gout (with which males preponderate notably).

*Age Incidence*—The ages of the patients on admission varied from 21 to 73 years (average age 42). The ages of the patients at the onset of their disease varied from 13 to 68 years, the average age was 34.9 years. The disease of 2 patients began at the age of 13 and 19 years, of 8, from 20 to 29, of 15, from 30 to 39, of 6, from 40 to 49, of 1, from 50 to 59, and of 2, from 60 to 69. Thus in about 70 per cent of the 34 cases the disease began when the patients were from 20 to 39 years of age.

*Duration of the Disease Prior to Admission to the Clinic, Total Number of Attacks*—Prior to admission to the Mayo Clinic the patients had had their disease for from four months to twenty-five years. The disease had been present twenty-one to twenty-five years in 2 cases, sixteen to twenty years in 2, eleven to fifteen years in 4, six to ten years in 11, one to five years in 10, less than one year in 5 (but there had

already been ten to one hundred and thirty attacks in each of these 5 cases). The 34 patients had had their disease for a total of about two hundred and forty-two years (average seven and two-tenths years).

The striking feature of the disease was the great frequency of irregularly recurring short attacks, each with its complete symptomatic remission. During their illness most of the patients had had scores and several had had "hundreds" of attacks. One patient (case 5), when asked to estimate how many attacks he had had within seven years, replied, "hundreds, perhaps thousands." Others replied, "hundreds—too many to remember" or "too numerous even to guess at." As stated, even the few patients who had had the disease less than one year had already had from ten to one hundred and thirty attacks. Thus in case 26 there had been twenty-three attacks in four months, in cases 21 and 29 ten and thirty-two attacks respectively in nine months, and in cases 15 and 19, fifty and one hundred and thirty attacks in eleven months. Omitting cases 1, 4, 5 and 16, in which there had been unnumbered hundreds of attacks, the total estimated number of attacks in the remaining 30 cases was from 4,930 to 5,320. Thus the average frequency was by the smallest reckoning, about one hundred and sixty-four attacks per patient during an average of about seven years of disease, that is, an average of about twenty-three attacks each year. Adding the 4 cases in which there had been "hundreds" of attacks, it is safe to say that the 34 patients had suffered about 7,500 attacks during their two hundred and forty-two years of disease, despite this the patients insisted that their joints always regained their normal appearance and function, a fact borne out by our own observations.

*General Frequency of Attacks*—The character of the individual attacks did not vary much, but the frequency and regularity of attacks varied greatly. The disease had notably changed its pace in 4 cases. In case 1 there had been almost daily attacks for two years and thereafter only four or five a year. In case 20 attacks came only three or four times a year at first and later weekly. One patient (case 32) had about two attacks a year for eight years, then the attacks stopped for six years, thereafter for eleven years he had two to four attacks yearly. In case 33 attacks came twice monthly at first and later almost daily. Thus the pace of the disease quickened notably in some and slowed in others.

In most cases, however, the pace of the disease had been relatively unchanged. To show frequency of attacks at the time of admission,

<sup>4</sup> We encountered 4 more typical cases in 1941, biopsy was made in 1 case between the patient's attacks. Articular tissues were grossly and histologically normal.

TABLE 1—An Oft Recurring Acute Disease of Joints (*Arthritis, Penarthritic, Para-Arthritic*) Apparently Producing No Articular Residue Synopsis of Thirty-Four Cases

Case	Date of Admission	Age, Yr	Sex	Duration of Disease Before Admission, Yr	Estimated Number of Attacks	Number of Joints Involved in Attack		Frequency of Attacks		Length of Attack		Interval Between Attacks		Sedimentation Rate, mm at 1 Hr	Uric Acid, Mg per 100 Cc of Whole Blood	Follow Up Condition as of April 1940 *
						Usual	Maximal	Usual	Maximal	Usual	Maximal	Usual	Maximal			
1	8/ 2/28	21	F	8	"Several hundred"	1	4 5	2 yr almost daily	12 36 hr	2 3 days	12 hr 1 wk	Few 24 hr	Few hr 2 days	3 4 4 0		Disease stopped spontaneously September 1928
2	1/11/31	49	M	6	50	1	1	6 yr 4 5 yearly	6 8 hr	6 8 hr	Hours 1 wk	2 3 mo	3 days sev mo	4 3		Still having repeated attacks
3	1/20/31	33	F	1	5	1	4	5 in year	4 5 days	4 5 days	1 10 days	1 mo	1 3 mo	3 1		Still repeated attacks but shorter (1 3 days)
4	5/21/31	32	F	8	Hundreds	1	1	Scores yearly	Several days	2 24 hr	Hours 2 days	"Few" 24 hr	Few hr few days	1 0		Attacks continue as before
5	7/22/31	32	M	7	"Hundreds, perhaps thousands"	1		Almost daily	2 24 hr	2 24 hr	Hours 2 days	Few 24 hr	Few hr 2 mo			Disease stopped spontaneously (?)
6	8/28/31	42	M	10	120	1	3	8 12 yearly	24 36 hr	24 36 hr	2 4 days	1 mo	4 6 wk	3 1		Disease stopped in 1933
7	2/22/32	32	F	11	200	1		About 2 monthly	8 48 hr	8 48 hr	8 hr 2 days	2 wk	3 days 4 mo	4 5		Disease stopped spontaneously in 1933
8	3/28/32	51	M	3	60	1 2		2 weekly	12 hr	12 hr	12 hr 2 days	2 3 days	2 4 days			
9	10/12/32	33	F	2 1/2	250	1										
10	8/ 6/35	34	M	15	750	1	2	1 2 weekly	36 48 hr	36 48 hr	2 8 days	2 5 days	1 day 5 mo	3 3		Attacks continue as before
11	11/11/35	39	F	2	300+	1		Almost daily	24 36 hr	24 36 hr	1 2 days	1 2 days	Few hr 3 days	19		Attacks same length but a little less frequent (3 4 weekly)
12	5/18/36	49	F	19	60	1	2	3 4 yearly	Few days	Few days	1 10 days	3 4 mo	2 10 days	7		Attacks more frequent (weekly) but of same duration, remissions still complete after 17 yr of disease
13	7/13/36	30	F	1 1/4	60	1	1	1 2 weekly	48 hr	48 hr	6 48 hr	2 4 days	2 10 days	12		Attacks shorter (4 8 hr) and a little less frequent (4 weekly)
14	7/31/36	45	M	21	750-800	1	1	3 monthly	48 hr	48 hr	2 3 days	10 14 days	1 45 days	4 0		Attacks same length but less frequent (4 5 yearly)
15	9/19/36	47	M	11 1/2	50	1	3	4 5 monthly	10 12 hr	10 12 hr	2 3 days	Few days	1 day 2 mo	3 5		Attacks same length but a little less frequent (3 4 weekly)
16	12/11/36	39	F	6	Hundreds	1	3	Almost daily	8 12 hr	8 12 hr	8 36 hr	Few 24 hr	Few hr 4 days	10, 12†		Attacks more frequent (weekly) but of same duration, remissions still complete after 17 yr of disease
17	3/15/37	50	M	14	60	1		3 4 yearly	24 48 hr	24 48 hr	1 4 days	3 mo	1 wk 4 mo	13, 25, 33†		Attacks shorter (4 8 hr) and a little less frequent (4 weekly)
18	3/15/37	41	F	3	180-200	1 3	5	1 yr 2 3 weekly	24 36 hr	24 36 hr	4 36 hr	1 2 days	Few hr 21 days	35†		Died 8 mo later (Sept 1938) of coronary thrombosis
19	7/ 9/37	32	M	11 1/2	130	1	8	2 yr almost daily	6 48 hr	6 48 hr	6 18 hr	Few 24 hr	Few hr 1 day	25†		Two attacks since dismissal, each lasting 12 hr
20	1/31/38	73	M	13	600 700	1	2	First 3 4 yearly	3 24 hr	3 24 hr	3 hr 3 days †	8 10 days	1 day 1 mo	54†		Attacks as frequent but a little shorter (6 24 hr)
21	2/14/38	51	F	7 1/4	10	1	1	Later weekly	2 3 days	2 3 days	1 3 days	1 wk	6 days 6 mo	14		Attacks shorter (only "overnight") and less frequent (monthly)
22	4/ 5/38	36	F	6	200 300	1 2		2 in 6 mo	24 hr	24 hr	6 hr 3 days	Few days		51		Attacks continue as before
23	5/16/38	25	F	3	100+	1	4	Every few days	3 6 days	3 6 days	6 hr 6 days	1 wk	6 10 days	3		Attacks shorter ("just overnight") but as frequent
24	7/12/38	19	M	10	100-200	1		Every few days	1 4 days	1 4 days	Hours 4 days	4 6 wk	Few days 6 wk	39		Attacks more frequent (almost daily)
25	10/24/38	53	F	6	45	1	3 4	6 8 yearly	2 days	2 days	1 2 days	1 day 4 wk	2 days 2 mo	35†		Attacks less frequent but of same length
26	1/13/39	10	F	1 1/2	23	2	2	Every few days	3 days	3 days	12 hr 3 days	Few days	Few hr 2 wk	35		Attacks about as before
27	1/23/39	11	F	2	100	1	3 4	Weekly	Few days	Few hr 3 wk	Few hr 3 wk	4 6 days	1 14 days	8†		Attacks less often (1 monthly) but of same length
28	3/29/39	63	F	16	300	1	3	Every 3 wk	36 hr	36 hr	1 4 days	1 day 4 wk	1 day 4 wk	31† 35†, 38†		Attacks shorter (4 hr) and less frequent ("seldom") but of same length
29	6/ 5/39	69	F	3 1/4	32	1 4		Weekly	1 2 days	1 2 days	1 2 days	1 3 wk	1 day 2 wk	27		Attacks more frequent (monthly) but of same length
30	6/22/39	95	M	6	150	1	3	2 monthly	2 3 days	2 3 days	1 7 days	1 day 2 wk		39		Attacks shorter (3 4 hr) and less frequent (2 3 weekly)
31	7/17/39	33	F	1 1/2	75	1	6	Weekly	36 hr	36 hr	12 hr 7 days	1 6 days	1 7 days	16†		Attacks shorter (3 4 hr) and less frequent (2 3 weekly)
32	8/ 8/39	59	M	25	50	1	3	8 yr, 2 yearly	12 24 hr	12 24 hr	12 hr 3 days	3 6 mo	1 day 8 mo	9		Attacks shorter (3 4 hr) and less frequent (2 3 weekly)
33	8/23/39	35	M	1 3/4	40	1	1	First 2 monthly	1 day	1 day	6 hr 3 days	1 3 wk	1 day 3 mo	22†		Attacks shorter (3 4 hr) and less frequent (2 3 weekly)
34	11/21/39	33	M	10	80 100	1	1	Now almost daily	24 48 hr	24 48 hr	12 hr 5 days	1 2 mo	1 day 4 mo	6, 30†		Attacks shorter (3 4 hr) and less frequent (2 3 weekly)

\* In all cases there were complete remissions after attacks  
† Sedimentation rate as attack subsided  
‡ This patient had serious coronary disease (infarct?)  
§ In this patient's first attack he was "in a hospital two weeks", the exact duration of attack is not known but presumably was several days, subsequent attacks were never longer than three days

the cases are tabulated (table 2) Nine patients were having few attacks, from two to ten, each year, 10, from eighteen to thirty-five, 7, from fifty to sixty, and 8, one hundred to two hundred and fifty or more Of the last 8 patients, 5 were having attacks almost daily They would escape an attack on some days, at other times they had a new attack every day, usually in a different site from that of the day before But even when the same joint was affected on two or more successive days the patients recognized the involvements as separate "attacks," because for at least a few hours each attack cleared up completely, leaving the joint "well" until the next attack These patients commonly stated that all morning, for example, their joints were entirely normal, then suddenly in the afternoon a joint would become swollen, red, painful and disabled, the involvement lasting a few hours and then disappearing completely in the evening or night Even if some hours or a day or two later another or the same joint was suddenly involved, their

TABLE 2—*Approximate Frequency and General Duration of Attacks on Patients' Admission*

Approximate Number of Attacks Each Year	Cases	Duration of Attacks, Days	Cases
250 or more *	5	1 or less	9
150-200	2	1 2	13
100	1	2 3	4
50-60	7	1 4	2
35	3	3-4	1
25	5	4 5	1
15	2	3 6	1
8-10	2	"A few"	2
6-8	2	"Several"	1
2-5	5		

\* Almost daily

conception of these short, isolated bouts as individual attacks seems justified

*Duration of Attacks*—The usual duration of the attacks is given in table 2 In 76 per cent (26) of the cases the attacks usually lasted only from a few hours to three days Despite their short duration, some of the very short attacks were painful The minimal length of attacks was three hours in case 20, four hours in case 18 and six hours in cases 13, 19, 22 and 23 The maximal duration of attacks was two days in 10 cases, three days in 7, four days in 5, five days in 1, about one week in 6, ten days in 1 and three weeks in 1 (in this case [case 27], however, many attacks lasted only a few hours) The maximal duration was unstated in 3 cases Thus in 67 per cent of the cases the longest attacks lasted only from two to five days Attacks longer than a week were exceptional

*Length of Intervals Between Attacks*—So varied and irregular was the pace of the disease in these cases that the intervals between attacks differed materially in different cases and from

time to time in the same case Most of the patients could not predict when the next attack would occur, in this disease there was no regularity to the attacks as in intermittent hydrarthrosis The usual interval was as follows only a few hours (one day or less) in 4 cases, one to two days in 2 cases, two to six days in 5 cases, about one to two weeks in 9 cases, "a few days" in 3 cases, one to two months in 5 cases, two to four months in 3 cases, three to six months in 1 case and unstated in 2 cases In 5 cases the intervals were on occasion (but not usually) fairly lengthy six months in cases 21 and 32, eight months in case 2 and a year in case 12 Having had two attacks yearly for eight years, 1 patient (case 32) experienced a spontaneous remission for six years before attacks returned

#### *Number of Joints Involved in an Attack*—

The number of joints affected in an attack was "usually only one" in 29 cases, "one or two" in 2 cases, from one to three in 1 case, two in 1 case and from one to four in 1 case The maximal number of joints affected in any one attack was one in 7 cases, two in 4 cases, three in 6 cases, three to four in 1 case and four or more in 7 cases, it was unstated in 9 cases In summary, the great majority of attacks were monarticular, 29 patients usually had only one joint affected, of these 29 patients, at least 7 never had more than one joint involved in any one attack

*Joints Involved*—The disease was ubiquitous, almost any joint in the body was liable to an attack At one time or another all patients experienced involvement of various finger joints, proximal interphalangeal joints most often, metacarpophalangeal less commonly and terminal phalangeal joints occasionally The dorsum of the hand was often affected The knees were affected at one time or another in 32 cases, the feet (various sites) in 25, the wrists in 23, the shoulders in 22, the ankles in 17, the elbows in 16, the jaws in 6, a sternoclavicular joint in 2 and cervical vertebral joints in 1 No patient specifically noted involvement of the lumbar or thoracic portion of the spinal column but 1 patient said his "spine" had been affected (unfortunately our record does not specify the site) Most of the patients had had from four to six (others had had from eight to eleven) different joints separately affected But in 1 case (case 28) only two sites, the fingers and knees, had been involved during three hundred attacks

*Joints Most Often Affected*—Patients repeatedly noted that, although any one of many joints had been affected during the years of their dis-

ease, 80 to 90 per cent of their attacks had involved one, two or three favorite sites. Joints most frequently affected were (in order of frequency) those of the fingers (proximal phalangeal or metacarpophalangeal, only occasionally terminal phalangeal), wrists, shoulders, knees, toes and elbows. The metatarsophalangeal joint of a great toe was the favorite site of attacks in 2 cases (cases 1 and 12).

#### FURTHER CHARACTERISTICS OF THE ARTICULAR ATTACKS

*Time of Onset*—In most cases attacks began any time of day or night. Two patients noted their attacks generally on waking at the usual morning hour, but 16 patients stated that most of their attacks came in the late afternoon or evening. Because of the vesperal nature of these attacks we missed seeing several of our outpatients during attacks which had practically disappeared by the next morning. In other cases in which such vesperal attacks occurred, we had to make special arrangements to obtain photographs or biopsies out of hours or to note the effect of such a medicament as epinephrine.

*Character of Onset*—The onset of attacks was generally described as sudden, 2 patients said their attacks developed instantaneously. Pain and swelling developed rapidly and were notable within "a matter of minutes" in 2 cases, within a half-hour in another case and within an hour or so in the others.

*Rapidity of Progression*—All attacks reached their maximal severity rapidly. In 2 cases within twenty-four hours and much more rapidly in the others. The maximal severity was generally reached in 1 case within half an hour, in 2 cases within one hour, in 4 cases within two hours, in 5 cases within two to four hours and in the rest "within a few hours."

*Severity and Character of Pain*—Pain varied considerably from case to case and in a given case from one attack to another. In 4 cases the pain was usually mild or moderate "a deep steady or throbbing ache", "a mild throbbing soreness", an "ache like a bad bruise." In most cases the pain was generally severe "a severe ache", "pain like a jumping toothache." One patient said her joints were "bursting with pain and too sore to touch." Several patients characterized the pain as "bursting," "a throbbing, knifelike pain" or a "tight, agonizing pain." One patient felt "as if my joints were grabbed within iron tongs." The pain was called "excruciating" by 3 patients and "vicious" by another. One patient was "almost delirious" with the pain. Two patients (cases 19 and 21) had mild or

moderate pain in many attacks but in others required morphine for relief.

In some cases the pain was more severe in the daytime, in 2 cases it was worse "in the evening", in some cases it was equally severe day and night, but in others it was at its maximum during the night and seriously interfered with sleep.

*Redness and Swelling*—In 5 of the cases the periarticular skin generally was not discolored during attacks, but in the other 29 cases articular redness of variable degree was present. It was often moderate but sometimes was pronounced "dark red", "fiery red", "as red as a strawberry."

Articular swelling varied notably, depending on the severity of the attack. The usual swelling was mild in only 4 cases and more severe in the rest. Particularly when finger joints were affected the swellings "flattened out the skin," "ironed the wrinkles out" or made the skin "tense," "shiny" or "waxy."

*Degree of Disability with Attacks*—The disability was mild or moderate in some cases and in some attacks, but it was generally considerable and limited the patient's activity. When joints of the upper extremities were affected, several patients could not dress themselves or work efficiently, they did their housework with difficulty, if at all, and "could not type" or play the piano. Some patients had to hold the hand or arm still, put it in a splint or move the affected hand with the other hand. When a foot or knee was affected some patients were only moderately disabled and could walk about in a slipper, perhaps with a limp. Some patients kept off their feet but were not actually confined to bed, 14, however, were so disabled they usually had to go to bed during attacks. One patient (case 18) was "completely disabled and couldn't do a thing," although her attacks were brief (four to thirty-six hours). A physician (case 20) considered several of his attacks sufficiently disabling to require hospitalization.

*Constitutional Reactions: Fever, Loss of Appetite or Weight*—There was little if any constitutional reaction during attacks. Despite their frequent severity they were afebrile. Although many of the patients had one or more attacks while under our observation, not one of them had fever therewith, including the one (case 16) who while under our observation had fifteen attacks within twenty-seven days.

Loss of appetite and weight are rather characteristic features of rheumatoid arthritis, but anorexia was not present in any of these cases. Twenty-five (74 per cent) of the 34 patients



had not lost weight (indeed some had gained) despite hundreds of attacks during their one hundred and sixty-eight years of illness.

It would appear, therefore, that significant loss of weight is not a characteristic feature of the disease.

*Involvement of Para-Articular Soft Tissues*  
*Para-Arthritis*—Ten (29 per cent) of the patients experienced recurring swellings of para-articular soft tissues. Some patients did not distinguish them clearly from the involvement of articular and periarticular tissues, because the para-articular swellings were often close to joints and often appeared during the articular attacks. Other patients carefully distinguished between the sites of attacks. The attacks of para-arthritis were recurrent but much less frequent than the articular attacks. Usually the para-arthritis appeared as a minor part of an articular attack, but the site of the former was often remote from the site of the latter. Sometimes the para-arthritis appeared without simultaneous arthritis. The attacks of para-arthritis generally came on rather suddenly, sometimes "out of a clear sky" or "within five minutes" and at other times more slowly. The size of swellings varied from the size of a dime ( $\frac{3}{4}$  inch [1.9 cm.] in diameter) to considerably larger. Redness was usually present, sometimes faint and at other times "fiery." Pain was sometimes mild but often severe, in cases 2 and 19 it was severe enough to require narcotics for relief. We observed one nocturnal attack involving the soft tissues of the upper part of an arm (case 28) in which the patient walked the floor because of severe pain. Slight pitting was occasionally present, but generally the swellings were rather firm and tender and did not pit appreciably. The attacks of para-arthritis lasted usually from six to twenty-four hours and then disappeared entirely.

Seven of the ten patients with para-arthritis (cases 5, 14, 16, 20, 25, 28 and 34) experienced such attacks while under our observation, sometimes with arthritis and at other times as isolated episodes without arthritis. The lesions we saw varied considerably in diameter (from 1 to  $1\frac{1}{2}$  inches or more [2.5 to 3.8 cm.]) and were usually red, tender and slightly elevated above the surrounding tissues. They disappeared within a few hours. The lesions in case 16 have been described in detail (figs 2*b* and 3*a*). These para-articular lesions were not notably affected by injections of epinephrine.

The lesions were, in our opinion, not truly those of angioneurotic edema or urticaria, although they resembled them somewhat. A dermatologic colleague described the lesions near a heel in case 5 as being "of an urticarial type,"

"not necessarily an allergic disease." The lesions of urticaria are characterized by the sudden appearance of smooth, slightly elevated patches somewhat whiter than the surrounding skin.<sup>5</sup> Those of angioneurotic edema may be tense and elastic or soft and pitting, the overlying skin may or may not be pink or dusky red.<sup>6</sup> The two conditions are closely related or according to some, identical. Some physicians consider angioneurotic edema to be a form of giant urticaria which tends to be localized to certain susceptible tissues and recurs in situ. Both urticaria and angioneurotic edema may produce itching, burning and stinging, but their lesions are not particularly tender or painful. Because the para-articular lesions present in our cases were generally tender and painful (sometimes narcotics were required for relief), we regarded them as distinctive lesions.

The sites of these para-articular swellings were, like those of the arthritis, varied, yet curiously consistent in that several patients described swellings identically situated. Usually only one and occasionally two or three sites were involved in each attack of para-arthritis. The sites of these para-articular lesions were as follows (in the order of frequency by case, not by attacks): internal or external malleolus in 4 cases, bottoms of the heels in 3, finger pads or distal phalanges in 3, the flexor surface of a forearm just proximal to the wrist (fig 2*b*) in 3, thumb pads (fig 3*a*) in 2 and the dorsal surface of a forearm just proximal to a wrist in 2, in 1 case each, a forearm just distal to the elbow, "anywhere on the palm of the hand," the left thenar eminence, the middle portion of the upper part of an arm, the medial aspect of the right thigh, the lateral aspect of a knee, a knee near the popliteal space, and the Achilles tendon.

In case 26 during many of the articular attacks a curious hoarseness without signs of a cold developed. Because of Solis-Cohen's<sup>1</sup> experience in 1 case we wondered whether the attacks of hoarseness might represent swellings of the cricoarytenoid cartilages analogous to those of articular and para-articular tissues.

*Intracutaneous or Subcutaneous Nodules*—The nodules in case 16 have been described (figs 1*a*, 3*a*, 5 and 7). In 2 other cases there were nodules. One patient (case 9) stated that with certain of her articular attacks localized asymmetric nodules developed in thumb pads or on

5 Dorland, W. A. N. *The American Illustrated Medical Dictionary*, ed 19, Philadelphia, W. B. Saunders Company, 1941.

6 Cecil, R. L. *A Textbook of Medicine*, ed 5, Philadelphia, W. B. Saunders Company, 1940.



fingers between joints. They were "smaller than a pea" and disappeared with the arthritis. She had none while at the clinic. In another patient (case 34), who frequently noted small, red, tender palmar "soie spots," a small, firm, freely movable subcutaneous nodule developed near a wrist, it disappeared in six or seven days.

*Relationship of the Various Lesions*—The three more common reactions, those in articular, periarticular and para-articular tissues, certainly appear to be closely related. The fourth, or rare, reaction, that producing nodules in intra-cutaneous or subcutaneous tissues, is also probably a part of the symptom complex. Perhaps it is merely coincidental, but more likely it is a feature of the more severe forms.

#### SUMMARY OF LABORATORY DATA

*Hemoglobin, Erythrocytes, Leukocytes*—Normal values for hemoglobin (for males 14 to 16.7 Gm and for females 13.5 to 15 Gm per hundred cubic centimeters of blood) and for erythrocytes (for males 4,500,000 to 5,000,000 and for females 4,000,000 to 4,500,000 per cubic millimeter of blood) were present in 29 (85 per cent) of the 34 cases. Two men had slight reductions in erythrocytes (case 2, 4,450,000, case 32, 4,370,000) but normal values for hemoglobin. One woman (case 12) had a slightly subnormal value for hemoglobin (13.3 Gm) but a normal number of erythrocytes. Only 2 patients had significant anemia. One, a woman (case 4), had 3,810,000 erythrocytes per cubic millimeter of blood and 12.3 Gm of hemoglobin per hundred cubic centimeters, the other, a man (case 20), had 4,010,000 erythrocytes and 12.9 Gm of hemoglobin, he had active coronary disease of which he died eight months later.

Total leukocyte counts made between attacks were normal (5,000 to 8,000 per cubic millimeter of blood) in 21 cases (62 per cent). They were slightly subnormal (3,800 to 4,700) in 3 cases (cases 22, 25, 32) and slightly elevated (9,100 to 16,800) in 10 (cases 10, 14, 15, 17, 18, 20, 24, 30, 33, 34). Total leukocyte counts made between attacks were normal in 12 cases, slightly low in 1 case and slightly elevated (9,500 to 12,400) in 6 cases. Similar counts made during attacks were normal in 4 cases and slightly elevated in 2 (9,600 to 12,400). In other words, the total leukocyte counts were generally normal both during and between attacks but were occasionally slightly or moderately elevated either during or between attacks.

Differential counts made in the intervals between attacks were normal in 9 cases and revealed slight lymphocytosis (36.5 to 48 per cent) in 9 and relative (and total) polymorpho-

nuclear leukocytosis (75 to 88 per cent) in 2. In only 3 cases were the percentages of eosinophils increased, and then but slightly (5.5, 6.5 and 10.5 per cent). Differential counts made during an attack were normal in 3 cases (mild or subsiding attacks) and revealed slight relative lymphocytosis in 2 cases and relative polymorphonuclear leukocytosis (68 to 72 per cent) in 3. Eosinophils were not increased in any case during an attack.

Counts of nonfilamented and filamented leukocytes were made in 12 cases. The percentage of nonfilamented cells was slightly increased (17.5 to 25) in 5, increased to 34.5 in 1 case (case 29) during a remission and normal (16 or less) in the rest.

In summary, total and differential leukocyte counts were often normal both during and between attacks, but there was a tendency toward relative lymphocytosis between attacks and either relative lymphocytosis or polymorphonuclear leukocytosis without eosinophilia during attacks.

One patient (case 16) seen both during and between attacks generally had mild relative lymphocytosis at both times. Another patient (case 19) had moderate lymphocytosis (48 per cent) with 13 per cent of the leukocytes nonfilamented cells between attacks and relative polymorphonuclear leukocytosis (68 per cent) with 23 per cent of the leukocytes nonfilamented cells during an attack, but the total leukocyte counts were normal throughout. In case 28 differential counts were normal between attacks and relative polymorphonuclear leukocytosis (71 to 72 per cent) was present during each of two attacks, the total leukocyte counts were always normal.

*Blood Uric Acid*—The concentration of blood uric acid was normal (1.6 to 4.5 mg per hundred cubic centimeters of whole blood) in 28 of the 30 cases in which it was estimated (table 1). In 2 cases the blood uric acid was slightly elevated: 4.9 mg in case 11 and 4.8 mg in case 20, in which heart disease was present. The average value of 32 tests done on 30 patients was 3.4 mg per hundred cubic centimeters of whole blood. Uric acid partitions (aerobic technic) in 6 cases were normal (table 3).

*Miscellaneous Tests on Blood*—The concentrations of various chemical constituents were as follows. Serum calcium was estimated in 13 cases, and the quantity was normal in all. Phosphorus was normal in 5 cases and slightly abnormal in 4 (2.7, 2.8, 4.4 and 2.6 mg per hundred cubic centimeters of serum). Phosphatase was normal in 3 cases. Cholesterol was normal (160 to 200 mg per hundred cubic centimeters of plasma) in 2 cases and somewhat elevated

(225 to 315 mg) in 9 Cholesterol esters were normal (110 to 145 mg per hundred cubic centimeters of plasma) in 1 case, slightly elevated (167 to 198 mg) in 7 cases and definitely elevated (277 mg) in case 27. Lecithin was normal (200 to 250 mg per hundred cubic centimeters of plasma) in 5 cases, slightly low (187 mg) in 1 case and slightly high (260 to 266 mg) in 3 cases. Fatty acids were normal (335 to 350 mg per hundred cubic centimeters of plasma) in 1 case and slightly low (280 and 312 mg) in 2 cases, but were increased in 7 (368, 379, 388, 404, 436, 439 and 569 mg). The total lipids were estimated in 10 cases and were normal (500 to 550 mg per hundred cubic centimeters of plasma) in none, they were low (455 mg) in case 16, during a mild attack, elevated (558 to 884 mg) in 9 cases (case 21, 448 mg, case 25, 640 mg, case 27, 884 mg, case 28, 709 mg, case 29, 703 mg, case 30, 598 mg, case 32, 641 mg, case 33, 629 mg, case 34, 564

24 mm (a much lower average than that in rheumatoid arthritis). Apparently the disease provokes only moderate and transient elevations in the sedimentation rate.

*Urimyses and Wassermann Tests*—These gave normal results in all cases.

*Roentgenograms*—Just as these patients did not have symptomatic residues despite their repeated attacks, roentgenographic residues did not develop in joints. Of the 164 roentgenograms of various joints made in the 34 cases, 150 (91 per cent) revealed nothing significant, the remaining 14 (9 per cent) showed changes regarded as unrelated to the chief complaint. The normal roentgenograms were of 44 hands, 20 wrists, 15 elbows, 10 shoulders, 17 feet, 14 ankles, 24 knees, 4 hips and 1 cervical portion and 1 lumbar portion of the spinal column. In many of these regions dozens, even scores, of attacks had occurred, not only were there no abnormalities in articular spaces or contour but there was no general or local decalcification. In some cases we took roentgenograms of as many as eight to twelve joints of a single patient yet found none that revealed anything significant.

Of the 14 roentgenograms that showed significant changes, 3 revealed simply alterations due to bunions, 2 revealed exostotic changes on the dorsa of great toes of 2 elderly patients, a not uncommon finding among elderly persons. The changes in 6 roentgenograms were interpreted as simply due to coincidental osteoarthritis (hypertrophic, senescent) as follows: in the hip and thumb bases of a man 73 years old (case 20) who had never had recurrent acute arthritis in his thumbs, in a hip of an obese woman aged 63, in a knee of a man aged 59, and in the fifth and sixth cervical vertebrae (the usual site for osteoarthritis of the neck) of an elderly woman. One patient who had had 60 recurrent attacks of acute arthritis of the hands, knees and shoulders showed no objective changes in these joints and no roentgenographic changes of his hands, a foot (in which he had *not* had acute recurrent arthritis) showed marked osteoporosis, he had injured this foot two months before and had had it in a cast. A woman aged 69 (case 29) had had acute recurrent arthritis three or four times in each shoulder and twenty or more times in her fingers and wrists, roentgenograms of the hands, the wrists and the right shoulder were normal, that of the left shoulder revealed calcified subdeltoid bursitis. The roentgenograms of a woman (case 12) who had had about sixty short acute attacks involving any one of many joints showed no articular changes in the elbows, hands, wrists, feet, knees or left shoulder, but

TABLE 3—Concentration of Uric Acid in Whole Blood, Plasma and Serum

Case	Uric Acid, Mg per 100 Cc		
	Whole Blood	Plasma	Serum *
16 †	3.1	4.4	5.0
19	3.8	4.0	5.2
29	2.7	2.8	3.0
30	3.9		5.2
33	3.7	5.0	5.3
34	4.3		5.4

\* Normal less than 6 mg

† The uric acid was estimated in this case during an attack, in the other cases, between attacks.

mg) In 8 of these 9 cases, the tests were done between attacks. Further studies will be made to determine the significance of this moderate hyperlipemia.

*Erythrocyte Sedimentation Rates*—Estimations of the sedimentation rate were made in 25 cases (table 1). The rate was normal (less than 20 mm in one hour, Westergren method) in 10 (40 per cent) of these cases, slightly increased (20 to 40 mm) in 12 and moderately increased (40 to 54 mm) in 3. Rates determined between attacks were normal in 8 cases and slightly to moderately elevated in 4. Rates determined during or just after attacks were generally but not always slightly increased. The tendency for rates to be normal between attacks but slightly increased during attacks is illustrated by the figures of cases 14, 17 and 34 (table 1). In case 16 the rate was 10 mm before an attack and only 12 mm during an attack. Among those cases in which rates were normal were some in which from one to several attacks a week were occurring and scores to hundreds of attacks had occurred. The average sedimentation rate for the 33 tests done on the 25 patients was only

there was notable toughening of the right acromion process, her history revealed that she had twice had a painful right shoulder for three months each time, an affair in contrast to her chief complaint of acute short recurring attacks in other joints

These few evidences of definite articular or osseous change give little support for the idea that the acute recurrent arthritis we are describing produces significant articular damage reflectible in roentgenograms. Since more than 90 per cent of all the roentgenograms of these patients failed to show abnormalities after a total of many decades of illness and hundreds of attacks, it must be concluded that the few articular changes noted were coincidental. When the temporary severity of the clinical symptoms and of the histologic reactions is considered, it is indeed surprising to find no significant roentgenographic residues

#### COMMENT ON PATHOLOGIC CHANGES OBSERVED

Our opportunities to study the pathologic changes of palindromic rheumatism have been limited to such gross observations as could be made at the time of biopsies and to histologic study of a few small fragments of tissue. We must acknowledge, therefore, that this experience may not have been sufficient to provide a complete picture of the pathologic processes which occur in this disease. When more material has been examined, some of our impressions regarding these pathologic processes may need revision.

The observations made to date may be summarized as follows

During an acute attack involving a joint there is rapid onset of acute inflammation with periarthral edema and gross thickening of the capsule of the joint. Polymorphonuclear leukocytes appear within the synovial membrane in large numbers, but eosinophils do not appear in significant numbers. A fibrinopurulent exudate may appear within the cavity of the joint. As the attack subsides the exudate is absorbed from the synovial fluid and the inflammatory cells clear from the synovial membrane. Then a brief period follows during which fibroblasts proliferate actively in the capsule and synovial membrane, but as the attack subsides the signs of inflammation in the capsule and synovia clear rapidly, and eventually the joint structures return to normal.

During intervals between attacks gross and histologic examination of joint tissues reveals no significant evidence of inflammation.

Tendon sheaths may be affected by similar sudden inflammation. During such an attack the walls of these structures show a nonspecific inflammatory process and excess fluid appears in the tendovaginal space. Cultures of this fluid and of the tissues from affected joints have remained sterile. The tendon sheaths, like the joints, are capable of returning to normal after the attack subsides.

The pathologic changes noted in these joints differed from those of rheumatoid arthritis in that no pannus was formed in the cases of palindromic rheumatism and no cartilage was destroyed. Furthermore, the inflammatory reaction within the capsular structures cleared completely once the attack subsided, a phenomenon we should not expect in rheumatoid arthritis. The follicle-like collections of lymphocytes believed by Allison and Ghormley<sup>7</sup> to be characteristic of the reaction in synovial membrane in cases of rheumatoid arthritis were not present in the synovial tissues in the cases of palindromic arthritis.

A subcutaneous nodule presented the histologic reaction of low grade nonspecific inflammation. Necrotic central zones surrounded by palisaded reticuloendothelial cells characterize the subcutaneous nodules of rheumatoid arthritis but were absent from this nodule. Nor did it show the fibrinoid degeneration or collections of cells resembling Aschoff bodies which are characteristic of the subcutaneous nodules of rheumatoid arthritis. The necrotic zones containing crystals of sodium urate which are characteristically present in the subcutaneous tophi of gout were not in evidence.

We cannot draw conclusions as to the possibility of the allergic nature of palindromic rheumatism from our histologic studies. It would be possible to point to certain similarities between the reactions we noted and the reported histologic reactions of urticarial wheals. Apparently a rapid exudation of fluid and inflammatory cells occurs in both conditions. Furthermore, complete and rapid resolution of the pathologic process may take place repeatedly in both conditions. The proliferative features noted in our specimens are not seen in the histologic reactions of wheals, and even were we to accept without question the similarities of these two processes we still should be doubtful as to whether palindromic rheumatism represents an allergic process, because many informed dermatologists today hold that urticaria is often a

7 Allison, N., and Ghormley, R. K. *Diagnosis in Joint Disease. A Clinical and Pathological Study of Arthritis*, New York, William Wood & Company, 1931.

manifestation of an infectious rather than an allergic process

True dermatologic allergy is probably best exemplified in the experimentally produced Arthus phenomenon, as described by Gerlach-Basel,<sup>8</sup> who did not find any specific histologic features and particularly denied the presence of eosinophils in his material

From these considerations, we can conclude only that palindromic rheumatism is caused by some unknown irritant

#### FACTORS PREDISPOSING TO OR PRECIPITATING ATTACKS

*Season and Weather*—In general attacks bore no seasonal relationships. Only 7 of the patients seemed affected by seasons, attacks were more common in winter in 2, in spring in 2, in summer in 2 and in autumn in 1

Apparently in only 4 cases were attacks more frequent or severe in cold, damp weather, the other patients noted no influence of weather on their disease

This relative absence of effect of season and weather on this disease is in notable contrast to conditions in rheumatoid arthritis

*Menses*—Three of the 19 female patients believed that their attacks were somewhat worse during menses, the rest saw no definite menstrual influence

*Work, Fatigue, Trauma*—In 2 cases attacks were said to be precipitated occasionally by overwork. The influence of work seemed especially definite in case 16, as described. The patient, a woman, did not entirely escape attacks when resting. She had mild attacks in the hospital when at rest and more severe attacks after deliberately spending long hours at occupational therapy. This state of affairs continued after she returned home, where also work seemed to be a dominant factor in the location and severity of attacks. Nervous or physical fatigue in 2 cases and slight trauma in 4 (for example, gripping the wheel of an automobile for several hours, a slight bruise) seemed to induce attacks, but in most cases neither work nor trauma was considered related to attacks

*Infection*—None of the patients related the attacks to any acute exogenous infection, and only 1 patient considered an infected focus (prostatitis) definitely related to attacks

*Food Sensitivity*—The majority of the patients could offer no explanation for their trouble, but 16 of them made a common sugges-

tion, that sooner or later they had come to suspect the factor of food poisoning or food sensitivity. They had each selected one or more foods as possible offenders, these they had avoided for varying periods. But when, despite this, attacks had continued, most of the patients had given up the idea, particularly because they found they could often eat the supposed offender with impunity. A few patients still held the notion, with varying degrees of conviction, that the attacks were related to food, but no one had been able to prove the point. The foods incriminated belonged to no one food group and need hardly be listed

#### AUTHORS' INVESTIGATIONS ON ETIOLOGY

When one of us (P S H) noted his first case of this condition, in 1928, and considered the nature of the attacks, their irregular frequency, sudden onset, short duration and complete remissions despite their relative violence the idea that they might represent some type of allergic reaction seemed attractive. In recent years several types of "allergic arthritis," generally chronic polyarthritis, sometimes acute monoarthritis or polyarthritis,<sup>9</sup> have been described. But no type of "allergic arthritis" has been definitely established, and the allergic nature of the conditions in the reported cases generally has been regarded as not proved.<sup>10</sup> We share this opinion because no incontrovertible evidence has been offered to indicate that the allegedly allergic acute or chronic arthritis could be consistently prevented or significantly modified by avoidance of the supposed antigen or that attacks could be repeatedly provoked by prescribing the antigen. Notwithstanding such skepticism, we reasoned that if there were such a thing as true allergic arthritis, perhaps this was it. Therefore, certain clinical and thera-

9 (a) Boemer, L C. Infection, Arthritis and Allergy with an Allergic Dietary Regimen, Illinois M J 75 474-475 (May) 1939. (b) Hench, P S, Bauer, W, Dawson, M H, Hall, F, Holbrook, W P, and Key, J A. The Problem of Rheumatism and Arthritis. Review of American and English Literature for 1937 (Fifth Rheumatism Review), Ann Int Med 12 1295-1374 (Feb) 1939. (c) Hench, P S, Bauer, W, Dawson, M H, Hall, F, Holbrook, W P, Key, J A, and McEwen, C. The Problem of Rheumatism and Arthritis. Review of American and English Literature for 1938 (Sixth Rheumatism Review), ibid 13 1655-1739 (March) 1940. (d) Wootton, W T. An Analysis and Discussion of Positive Food Reactions in Five Hundred Individuals Afflicted with Arthritis or Rheumatoid Conditions, J Arkansas M Soc 36 67-69 (Aug) 1939.

10 Boemer<sup>9a</sup> Hench and others<sup>9b</sup> Bauer, W and Short, C L. The Treatment of the Arthritides of Known Origin, New England J Med 223 286-293 (Aug 22) 1940.

8 Gerlach-Basel. Ueber Beziehungen der Entzündung zum anaphylaktischen Zustand, Verhandl d deutsch path Gesellsch 19 126-131, 1923.

peutic investigations were made in an attempt to prove or disprove the hypothesis

*Does the Disease Represent an Allergic Reaction in Joints?*—Familial allergy was not obvious in 24 cases, but 17 close relatives of the remaining 10 patients suffered as follows: 6 from asthma, 3 from hay fever, 3 from known sensitivity to foods (hives), 2 from urticaria of unknown origin, 2 from "eczema" and 1 from migraine. As to the patients themselves, 16 did not have allergic reactions of any sort, 6 had nothing but occasional migraine unrelated to the arthritis and 1 became "dizzy" after taking acetylsalicylic acid. One patient had had attacks of angioneurotic edema two and four years before the onset of his arthritis but none since. Four patients had had occasional attacks due to food sensitivity (abdominal pain, nausea, vomiting and diarrhea beginning within one hour after eating milk, sea food, prunes, oysters or spinach), 1 of these patients also had occasional migraine and another hay fever and asthma. In none of these 4 patients did the articular and gastrointestinal symptoms ever coincide. Six of the patients had had "hives" (urticaria), in 4 of these the hives occurred occasionally and never with arthritis. In 2 cases the attacks of hives generally did not, but occasionally did, coincide with articular attacks, the coincidence was so infrequent that both patients (cases 1 and 15) considered them probably unrelated.

In summary, 16 of the patients had no clinical signs of allergy, and 18 experienced a total of 21 varied possibly allergic reactions. This is not an unusual number to be found among 34 patients of any sort, and the fact that none of the established allergic reactions occurred regularly with the articular reactions seems to speak for the independence of the two conditions.

In 28 cases cutaneous tests were made with various antigens: the common inhalant group, a group of foods to which allergic patients are commonly sensitive, and others including those which the patients themselves suspected might be related to their arthritis. Results were entirely negative in 10 cases and negative except for a few slight reactions in 12 other cases. Such minor reactions were considered of little or no significance, and none of the foods suspected by the patients caused positive cutaneous reactions. Cutaneous reactions of grade 2 developed in only 5 cases, reactions of grade 3 to beef and lamb developed in 1 case. Many of the patients were fed large amounts of the foods to which they were sensitive (even if the reaction was only of grade 1) as well as the foods of which they were suspicious but to which their skin was not sensitive. In no case could we prove to our

satisfaction any provocative effect of these foods as far as joints were concerned. Despite the negative reactions to provocative tests, 9 patients accepted a therapeutic test, avoiding the suspected foods for variable periods, only 1 patient believed that the disease was significantly modified thereby.

In a few cases we attempted without success to provoke an attack by histamine, giving a fairly large single (1 mg.) dose intravenously. Results of cold allergy tests made in 5 cases were all negative. One patient (case 2) insisted (and still does) that his attacks were shortened by injections of epinephrine hydrochloride, but such injections in several other cases did not significantly alter the duration or severity of attacks seen by us. As will be noted later, our results with histamine desensitization or with histamine given orally have not been impressive.

Points favoring an allergic hypothesis were (1) the suggestive nature of the attacks and their sudden appearance and disappearance without residues, (2) the impressions of several patients that their attacks were caused by certain foods, (3) the occasional presence of clinical allergy of patients and their relatives, and (4) the occasional occurrence of arthritis and hives or angioneurotic edema in the same case. Points against an allergic hypothesis were (1) the complete absence of orthodox clinical allergy in 47 per cent and the absence of familial allergy in 71 per cent of the cases, (2) the generally negative cutaneous reactions (in 79 per cent of the patients tested), (3) the absence of eosinophilia in blood or affected tissue, (4) the negative results of provocative and therapeutic tests involving suspected foods, (5) the generally negative effect of epinephrine, (6) the negative provocative effect of histamine in large doses and (7) the essentially negative therapeutic effect of histamine desensitization. Dr. L. E. Prickman, who sees much allergic disease at the Mayo Clinic, saw many of these patients with us. In discussing them he recently stated: "The evidence at present points away from an allergic basis for the disease."<sup>11</sup>

*Is the Articular Reaction Due to Infection?*—The attacks bore no apparent relationship to acute exogenous infection, such as sore throat or influenza. Most of the patients had long since been relieved of infected foci with no or only temporary relief. Only a few infected foci still remained. Tonsils had already been removed in 32 cases (cleanly in 29, with small tags remaining in 3). Moderate infection was

<sup>11</sup> Prickman, L. E., in discussion on Hench, P. S., and Rosenberg, E. F. Palindromic Rheumatism, Proc. Staff Meet., Mayo Clin. 16: 815 (Dec. 17) 1941.



present in the 2 surviving pairs of tonsils. The entire group had only 4 dead teeth, 3 roots (1 infected) and 3 infected teeth, 15 patients had slight pyorrhea. Among the 19 females were 3 with cervicitis and 3 with cervical erosions. Prostatitis of significant degrees was found in only 4 of the 15 men. Prostatic cultures from 1 patient revealed only *Corynebacterium xerosis* (diphtheroids). Another patient, a physician with prostatitis grade 4, regarded prostatic massage as a frequent provocative of his attacks. In his case prostatic cultures revealed micrococci and a few streptococci. The same patient had sinusitis, the only instance of this in the entire group.

In a few cases cultures of the nasopharynx were made. In some no significant organisms were recovered. In others hemolytic streptococci were found, but they generally did not produce positive cutaneous reactions in these cases or significant lesions in animals. In 1 case green-producing streptococci from the nasopharynx injected into rabbits produced some periarticular but no other lesions. Green-producing streptococci (from the nasopharynx) in another case (case 20) also produced hemorrhagic muscular and periarticular lesions in rabbits.

Among the several patients who had infected foci removed as therapeutic tests, only 1 (case 23) considered results moderately successful, after tonsillectomy her attacks were milder and less frequent.

Cultures of affected tissues removed at biopsy in 4 cases revealed no bacteria. Agglutination tests for *Brucella abortus* were negative in 4 cases and slightly positive (1/80) in 1 case, the latter test was considered of no significance.

*Does the Disease Represent Angioneurosis?*—Dorland's<sup>5</sup> definition of angioneurosis as "any neurosis affecting primarily blood vessels, a disorder of the vasomotor system, as angiospasm, angioparesis, or angioparalysis" illustrates the tenuousness of the entire concept of angioneurosis. Within this generic concept have been included a great variety of syndromes whose only relationship consists in the fact that affected patients display a tendency for blood vessels to react to unknown stimuli by contracting, by dilating or by alternately contracting and dilating. Under this title are grouped such varying conditions as angioneurotic edema, urticaria, intermittent hydrops, scleroderma, erythromelalgia, acroparesthesia, Raynaud's syndrome and many other conditions. Patients affected with angioneurotic disorders are said to be subject to paresthesias, cyanosis or pallor of the fingers and toes, hyperhidrosis, "trophic disorders" of the skin, hair, nails and teeth, increased oculocardiac and

vagus reflexes, blushing and pallor of the face.<sup>12</sup> These stigmas of angioneurosis were not significantly present among our patients. Therefore we could not conclude that "angioneurosis" was the cause of the articular and other reactions of palindromic rheumatism.

#### DIFFERENTIAL DIAGNOSIS

*Rheumatoid (Chronic Infectious, Atrophic, Proliferative) Arthritis*—Two varieties of this disease are described, but palindromic rheumatism resembles neither variety. The first, or common, variety (typical, ordinary or primary rheumatoid or atrophic arthritis) generally attacks thin, viscerotropic persons with vasomotor instability. It attacks females two or three times as often as males, it usually affects small joints first and then progresses slowly and rather symmetrically to involve larger, less peripheral joints. Joints are swollen and sore with little if any redness. Little or no fever occurs, and signs of subacute inflammation are usually absent. Partial remissions are frequent, but complete remissions are rare. Sedimentation rates soon increase, sometimes within three weeks of the onset of the disease. Secondary anemia, a slight reduction in blood fats and loss of weight and appetite commonly appear. Roentgenograms soon reveal general decalcification, and within a few months or so more notable changes result from synovial proliferation and destruction of cartilage.

The second, or less common, variety is called "atypical" or "secondary rheumatoid" (or atrophic) arthritis. By those who consider it not a variety but a separate disease, it is called "infective arthritis" or "focal arthritis."<sup>13</sup> Its onset is more acute or subacute than is the usual onset of "primary rheumatoid arthritis", it appears at times after a definite infection, such as influenza, acute tonsillitis or pharyngitis. A few small or large joints are asymmetrically affected. The disease may progress rapidly, but remissions are supposedly more frequent and more complete than in the first variety. Fever may be present, with considerable articular warmth, redness, swelling and other constitutional signs of infection or toxemia. Roentgenograms at first reveal local articular, rather than general, decalcification but later show articular disintegration similar to that in the first variety.

<sup>12</sup> Sachs, B., and Hausman, L. *Nervous and Mental Disorders from Birth Through Adolescence*, New York, Paul B. Hoeber, 1926, p. 701.

<sup>13</sup> Hench, P. S., Bauer, W., Fletcher, A. A., Ghrist, D., Hall, F., and White, T. P. *The Problem of Rheumatism and Arthritis. Review of American and English Literature for 1935* (Third Rheumatism Review), *Ann Int Med* **10**: 754-909 (Dec.) 1936. Hench and others<sup>9b, c</sup>



Even those who make the greatest distinction between these two conditions agree that the end results are about the same and that no pathologic distinction can be made. Both lead sooner or later to chronic progressive arthritis with articular destruction and deformity. The dominant feature in either variety is the great tendency toward a deforming arthritis with no complete remissions. Even in those cases in which the disease begins with a few preliminary skirmishes and rather complete remissions before becoming progressively chronic, these individual skirmishes last, not hours or days, but weeks or months.

The chief points which distinguish our cases of palindromic rheumatism from instances of rheumatoid arthritis include the following: (1) the totally different pattern of the arthritis (one of numerous short attacks and persistent functional restitution), (2) the tendency for only one or two joints to be involved in an attack, (3) the frequent isolated short attacks of para-arthritis, (4) the general absence of significant constitutional reactions, (5) the relative absence of effect of season and weather, (6) the sedimentation rate, which is relatively normal or only moderately and transiently elevated, (7) the moderate increase (rather than decrease) in blood fats, (8) the persistently negative roentgenograms, and (9) the different pathologic reaction. The greatest and most convincing difference is the persistent absence of chronic arthritis even after scores or hundreds of attacks and years of disease.

It may be argued that, despite these obvious differences between palindromic rheumatism and rheumatoid arthritis, palindromic rheumatism may be merely a newly described variety of rheumatoid arthritis. It may be argued that the differences between the two clinical pictures are no greater than those between, for example, clinically active and progressive tuberculosis in 1 case and a small healed Ghon complex in another. It might be suggested that perhaps the distinctions between palindromic rheumatism and rheumatoid arthritis result, not from any dissimilarity in the causal agents of the two conditions, but from different tissue reactions or immune responses of the host. This argument will gain force only if prolonged study of our cases and of similar cases indicates that chronic articular residues with pathologic reactions indistinguishable from those of classic rheumatoid arthritis do eventually develop in a notable number of cases of our palindromic rheumatism. On the basis of our experience<sup>14</sup> to date we do not consider

palindromic rheumatism merely a newly described "palindromic variety" of rheumatoid arthritis.

*Periarticular Fibrositis*—The four commonest articular diseases which attack joints repeatedly and then disappear completely are periarticular fibrositis, intermittent hydarthrosis, rheumatic fever and gout. Obviously our cases did not represent ordinary primary fibrositis. In this condition there are practically no redness or swelling of joints, no recurrent para-articular swelling and no seropurulent exudate.

*Intermittent Hydarthrosis*—This disease rarely affects any joint but knees, is rarely painful and attacks joints at regularly spaced intervals. Its pattern and progression are different from those which we have described for palindromic rheumatism. In our cases of palindromic rheumatism a transient intra-articular exudate was sometimes present but was overshadowed by the more noticeable periarticular inflammation, and the attacks were irregularly, not regularly, spaced.

*Rheumatic Fever*—This is characterized by recurrent attacks of acute febrile polyarthritis of some weeks' duration with residual carditis. In our cases attacks were afebrile, short and usually monoarticular, and carditis was absent in all cases, even those of many years' duration.

*Gout*—Our cases presented certain features suggestive of acute gouty arthritis: the sudden onset of the attacks, appearing sometimes during the night, the rapid progression to maximal disability, the occasional involvement of great toes, the pain, which was often severe and sometimes worse at night, and the rapidity and completeness of the remissions. But none of our patients had hyperuricemia, tophi on the ears, urates in the joint tissues or the roentgenographic changes of gout even after years of disease. Nor were any of our patients relieved by a regimen for gout or made worse by high purine, high fat diets. In our cases the attacks were generally much shorter and much more frequent than even those of severe, progressive gout. Had gout been present, its characteristic features surely would have developed in some cases after so many attacks.

*Angioneural Arthrosis (Solis-Cohen)*—While continuing our search for a report of a condition resembling ours, in 1935 we came on a relatively old clinical description of cases somewhat resembling ours, a report by Solis-Cohen of a condition which he called angioneural arthrosis

<sup>14</sup> Hench, P. S., in discussion on Hench, P. S., An Oft Recurring Disease of Joints (Arthritis, Peri-

arthritis, Para-Arthritis) Apparently Producing No Articular Residues, J. A. M. A. **115** 2208 (Dec. 21) 1940.

(periarthrosis, "pararthrosis") and which he believed to be commonly mistaken for gout or rheumatism. He reported 6 cases in 1911 and 21 more in 1913. His reports unfortunately escaped the attention not only of internists but of rheumatologists as well. In these cases painful swelling in and around joints appeared at regular or irregular intervals. Affected were joints alone in 11 per cent, soft tissues alone in 30 per cent and both joints and nearby soft tissues in 59 per cent of the 27 cases. The individual attacks lasted from a few hours to many weeks and then disappeared completely. Attacks were polyarticular in 70 per cent and monoarticular in 30 per cent of cases. Almost any joint was liable to involvement, but especially the more peripheral joints—fingers, wrists, elbows, toes or a big toe, ankles and knees. No joint was immune, vertebral and temporomaxillary joints were sometimes involved. In one case laryngoscopic examination revealed involvement of the cricoarytenoid cartilages. The intervals between attacks were regular in some cases and irregular in others and lasted from a few days or weeks to months or years. Thus attacks came daily or weekly in some cases and only four or five times a year in others. Spontaneous remissions for months or years occasionally occurred. Solis-Cohen's 27 patients had had a total of 110 (average 4) attacks (a much smaller average than in our cases). The sex incidence was 45 per cent males and 55 per cent females. Thirty per cent of his patients were less than 12 years of age, 45 per cent, from 12 to 25, 18 per cent, from 25 to 50, and 7 per cent, from 50 to 70. It is not stated whether this refers to the ages of the patients when first affected or when first seen by Solis-Cohen.

The swellings were ascribed either to intra-articular effusions or to nonpitting edema of periarticular tissues or to both. They were generally but not always painful, pain being moderate to agonizing. They were generally associated with red or cyanotic discoloration of the skin, occasionally with eruptions (vesicles, bullae) and also with a subjective (but not an objective) sensation of local heat. Fever was never present in 60 per cent of the cases but was present in some attacks in 22 per cent and in all attacks in 18 per cent. When present the fever was "continuous, recurrent or intermittent." It was irregular and "utterly capricious" in some cases and paroxysmal and "apparently periodic" in others. Fever lasted for a few (twelve to seventy-two) hours or a few days. It was inferred that eosinophilia or leukopenia was sometimes present. Many of the patients presented "the typical dermatographic, ocular and nail-bed

signs" of vasomotor or autonomic ataxia. Exacerbants of the attacks were fatigue, emotion, toxemia and atmospheric changes.

Solis-Cohen regarded this condition as one species of autonomic ataxia, a "slighter form" of articular reaction than intermittent hydrarthrosis. To him the articular attacks represented recurrent angioneurotic crises in cases in which the characteristic stigmas of angioneural imbalance were present. He made no articular biopsies but interpreted the effusions as due to angioneurotic edema, in angioneural arthroses "we are not dealing with a true inflammation-arthritis." Treatment was based on this concept and included for the acute stage local and sometimes general rest, a liquid or soft diet and "elimination", for the convalescent stage "roborants

TABLE 4—*Points of Difference Between Authors' Cases and Those of Solis-Cohen and of Kahlmeter*

	Cases of Solis-Cohen ("Angioneural Arthrosis")	Cases of Kahlmeter ("Allergic Rheumatism?")	Our Cases (Palindromic Rheumatism)
Patients less than 12 years of age	30%		None
Polyarticular attacks	70%	Few	Few
Fever	40%	Occasional	None
Cutaneous eruptions	Occasionally erythema, vesicles, bullae	Occasionally crysipeloid rash	None
Duration of attacks	Sometimes "many weeks"	Rarely more than 1 week	Rarely 1 week
Intervals	Sometimes regular	Irregular	Irregular
Allergic reactions	Common	Common	Rare
Pathologic reaction in joints	"Transudate" (assumption)	Serous exudate (assumption)	Inflammatory exudate

and hematinics", between attacks measures to "re-educate vascular reactions" and to "restore vasomotor tone."

Our cases resemble these in many respects, but certain noteworthy differences are apparent (table 4). 1 In Solis-Cohen's cases "the chief symptomatic elements were pain, swelling, discoloration and fever." Forty per cent of his patients had fever in some or all of their attacks. None of our patients had fever during their attacks. 2 In Solis-Cohen's cases the attacks sometimes lasted "many weeks", in our cases, only a few hours or days, rarely more than a week. 3 In Solis-Cohen's cases attacks were polyarticular in 70 per cent and monoarticular in 30 per cent. In our cases the majority of attacks were monoarticular. 4 Solis-Cohen emphasized the frequent occurrence of hives, dermatographism and other evidences of vasomotor ataxia in his cases and also the occasional presence of vesicular or bullous cutaneous lesions. Our patients

exhibited no vesicles or bullae, 20 per cent had had hives or angioneurotic edema at some time or other, but rarely accompanying their attacks of arthritis. 5 In 30 per cent of Solis-Cohen's cases the disease developed before the age of 12 years, this was true in none of our cases. 6 Solis-Cohen considered the exudation to be a transudate or an edema and the articular reaction to be, not true inflammation, not arthritis, but "arthrosis." He presented no pathologic data on his cases and hence could not prove his concept. Our data reveal the presence of a true inflammatory exudate, therefore the term "arthrosis" is inappropriate, at least for our cases.

Despite these important differences the resemblances between the two conditions are too great to be dismissed lightly. Solis-Cohen presented no photographs or roentgenograms of his cases and no data on pathologic changes or on blood urates (the latter were hardly available in 1913). Perhaps he noted some cases similar to ours but adulterated his description of them by including some extraneous cases. If this is not so, we cannot, on the basis of our experience to date, identify the condition in our cases with his disease which was so often febrile and polyarticular.<sup>15</sup>

"*Allergic Rheumatism*" (Kahlmeter) — Although, with others, Kahlmeter<sup>2</sup> generally regarded the so-called allergic types of arthritis skeptically, in 1939 he noted one form which he considered might be truly allergic. Under the term *rhumatisme articulaire et périarticulaire d'une nature réellement allergique* he described 54 cases observed within five years. Twenty-two per cent of the patients were males and 78 per cent females. Most of them were less than 50 years of age, 40 per cent were from 31 to 40 years. Attacks of "local edema" involving articular or periarticular tissues, tendons or subcutaneous connective tissue distant from joints recurred at irregular intervals. No articular biopsies were made. The edema was assumed to be a serous, not an inflammatory, exudate, and there was neither local heat nor redness. The location of the edema was capricious, but usually only one or two joints or adjacent sites were affected at a given time. Articular swellings were often afebrile, sometimes associated with a mild fleeting fever and an erysipeloid or erysi-

pelatous skin rash. The attacks lasted generally from several (twenty-four to forty-eight) hours to several days, occasionally seven to fourteen days, and then invariably disappeared completely, leaving no subjective or objective residues—"certainly no progressive joint lesion." The intervals between attacks were from one or two days to several months.

Allergic reactions were common among the relatives as well as among the patients themselves, in most of whom the articular attacks alternated or coincided with certain allergic reactions. Of these patients, 35 per cent had had urticaria, 13 per cent asthma, 11 per cent Quincke's edema and 9 per cent migraine. Some patients noted nausea, diarrhea or lassitude for a day before attacks. Eight cases in which the condition had been present for from one to twenty years were described briefly. A mildly febrile urticaria which after a few days was associated with edematous swelling of one or two finger joints or tendon sheaths developed frequently in 1 case, "several days" later the urticaria, fever and arthritis disappeared together. In Kahlmeter's cases there was no anemia, total leukocyte counts were normal or somewhat low (about 5,000), there was a "constant" relative lymphocytosis (38 to 52 per cent) without eosinophilia (1 to 2 per cent). Sedimentation rates were normal or only mildly and fleetingly elevated during attacks (the highest value mentioned was 33 mm). No data on pathologic changes or roentgenograms were given. With reservations Kahlmeter regarded the condition as allergic because of the frequent allergic reactions of patients and their relatives and because tuberculin, Dick and Schick tests revealed notable hypersensitivity of the skin—"nonspecific allergic reactions." Despite this Kahlmeter was sufficiently uncertain of the cause of the disease to express the title of his paper in the form of a query "Are There Forms of Articular and Periarticular Rheumatism of a Nature Truly Allergic?" The matter of sensitivity to food was not considered. One patient was given injections of tuberculin in "homeopathic doses" (0.5 cu mm) during twelve weeks. An attack developed regularly two days after each injection, but the duration of attacks was gradually shortened from several days to two hours and then the attacks disappeared. Three patients were given ten injections of sodium keratinate, which were assumed successful in stopping the disease.

These cases resemble ours even more than those of Solis-Cohen (table 4), but again certain differences must be noted. Local redness was

15 On Jan 8, 1942, Dr Solis-Cohen wrote the authors "At first sight the two groups of cases [that described by Solis-Cohen and that described herein] seem to differ in so many important particulars that they may be provisionally classified as, at least, different varieties."

usually absent in Kahlmeter's cases, it was usually present in ours. Kahlmeter's patients occasionally had fever and erysipeloid rashes, none of ours did. The frequency of the common allergic reactions was much greater in his cases than in ours.

The similarities between Solis-Cohen's, Kahlmeter's and our groups of cases are more striking than their differences. Perhaps they represent the same disease. Perhaps further experience will bring us cases with the missing features (fever, rashes, impressively coincidental acute allergy, and so forth), or perhaps pruning and more rigorous selection of cases by Solis-Cohen and Kahlmeter will remove the differences, but for the present the differences should be noted.

#### PROPOSED TERMINOLOGY

Were we prepared to assume (which we cannot yet do) that our cases were instances of the same condition as the "angioneural arthrosis" of Solis-Cohen or the "allergic rheumatism" of Kahlmeter, we still could not approve the adoption of either of these two terms for the disease we are describing, because the presence of an angioneurosis or of an allergic reaction as the basic cause remains unproved. We have avoided the use of a term which would commit us to an unproved etiologic concept. Furthermore, the term "arthrosis" is not suitable for a condition a feature of which is a true inflammatory exudate. Vague though it is, the term "rheumatism" (used in the broad American, and not in the specific English, sense) seems more suitable than "arthritis," because the former term is more comprehensive and hence more applicable to a condition which produces not just arthritis but also peri-arthritis, para-arthritis and occasionally subcutaneous nodules. Such simple terms as "recurrent rheumatism," "intermittent rheumatism" or "remitting rheumatism" are unsatisfactory for our disease because they are either too nonspecific and indefinite or too suggestive of recurrent rheumatic fever or intermittent hydrarthrosis. The nicknames "hit and run rheumatism" and "phantom rheumatism" proved useful for a time to satisfy the curiosity of patients and their natural desire for at least a name for their disease, but such nicknames are of course unsuitable as permanent designations.

When an etiologic term cannot be applied, a distinctive descriptive term should be used. Such a designation we found in the term "palindromic rheumatism," suggested to us by Profs. A. D. Fraser and Atcheson L. Hench, of the departments of ancient languages and English literature, respectively, of the University of Virginia.

"Palindromic" means simply "recurring" or "returning" and is so defined in current non-medical and medical dictionaries. It is derived from the Greek word *παλινδρομέω* which means literally "to run back." The verb and its related adjective and noun were used by Hippocrates<sup>16</sup> or by his contemporaries. Used in a strictly non-specific sense, they are found, not in the Hippocratic canon, the proved writings of Hippocrates, but in the Hippocratic corpus, the body of writings ascribed to Hippocrates, some of which may have been written by his contemporaries. In "De morbis vulgaribus" the Hippocratic writer used the adjective "palindromic" referring to recurring erysipelas or to recurring, retreating or subsiding abscesses. Prof. James Constantine, of the University of Virginia, helped us to trace and define later uses of the term. The medieval Byzantine scholar Hesychius used the word as meaning to recur or retreat, when applied to disease it designated one which either returned or disappeared. The new Liddell and Scott Greek lexicon<sup>17</sup> defines palindromic, used in a medical sense, as meaning "recurring" or "subsiding without coming to a head."

Since the most obvious and characteristic features of the condition we have described are its frequent recurrences, its attacks and retreats, the term "palindromic" seems indeed fitting as it is descriptive, yet sufficiently unused in recent writings to be distinctive to modern ears. Hence we propose to use in a specific sense, that is, for this specific condition, this term heretofore used by Hippocrates and other writers in a non-specific sense. As one of our advisers aptly said, "What was good enough for Hippocrates ought to be good enough for you." The designation "palindromic rheumatism" has been approved for inclusion in the "Standard Nomenclature of Disease" and appears, with numerical designation, in the third edition. We believe it will be useful and satisfactory until a better (etiologic) term can be applied.

#### TREATMENT

Numerous treatments had been used by our patients before their coming to the clinic, generally without success, they included removal of infected foci and use of vaccines, bee venom and various medicines. Most of the patients had fallen back on the use of heat and analgesics during attacks.

16 Hippocrates. *De morbis vulgaribus*, liber secundus, in *Opera omnia*, translated and edited by A. Foësius, Geneva, S. Chouet, 1657, p. 1035, *Oeconomica Hippocratis alphabeti serie distincta*, ibid., 1662, p. 289.

17 Liddell, H. G., and Scott, R. *A Greek-English Lexicon*, revised and augmented by H. S. Jones, Oxford, Clarendon Press, 1940, vol. 2, p. 1292.

Our first remedies were predicated on the idea that the disease might be allergic, later, measures to combat some possible infection were instituted. Neither plan of attack has produced notable results, as the follow-up data in table 1 indicate. Our results with epinephrine, ephedrine, amphetamine, ergotamine tartrate, diets low in purine, diets free of supposed food antigens, removal of infected foci and autogenous vaccines have all been relatively unsuccessful. Histaminase was used without results in 3 cases. Histamine desensitization has given definitely negative results for 3 patients and equivocal results for 4 others, who, however, insisted that their attacks had become less severe or less frequent since histamine was used. Further observations are necessary before making a final evaluation. Some patients have continued to rely on diathermy, hot packs or other forms of heat. Injections of triple typhoid vaccine may have been responsible for the temporary relief noted in case 16.

A few remedies used by certain patients since their dismissal from the clinic are worthy of comment. Sulfanilamide did not affect the disease in 2 cases (cases 20 and 34). One patient (case 17) felt "75 per cent better for a year" after having fever therapy, but he still has his attacks. One patient (case 13) thought she was partially relieved by taking "dicalcium wafers," and another patient (case 8), a physician, ascribed the temporary disappearance of his disease to the daily use of 75 to 100 grams (4.8 to 6.5 Gm.) of calcium gluconate, later the disease recurred only to disappear completely again after total alveolectomy. One patient (case 5), who ascribed his attacks to nervous fatigue, wrote that his attacks are less severe since he "quit the oil business, became a druggist and began to take phenobarbital daily." Another patient successfully employed an even more novel remedy. She adopted a baby, quit worrying about herself and lost her attacks. Her statement is food for thought.

#### PROGNOSIS    END RESULTS

Our follow-up study has revealed the following facts. In 4 cases the patients obtained an apparent "cure" within a few months after leaving the clinic and have had no further attacks for from seven to eleven years. Cessation of the attacks occurred spontaneously in 3 of these cases and presumably as a result of treatment with calcium gluconate or of alveolectomy in the other. In 5 cases attacks have become shorter and less frequent, in 1 of these the patient, a local resident, is apparently obtaining a spontaneous cure. His attacks are becoming much milder and much less frequent. In 3 cases attacks are shorter but as frequent as always. In 4 cases attacks are less frequent but their duration remains the same. The condition of 7 patients remains unchanged as to frequency, severity and duration of attacks. Three patients are perhaps worse in that their attacks are more frequent although not longer. One patient died of coronary disease. Seven patients have not answered our inquiries.

Thus of the 27 patients of whose condition we know, 15 per cent are now well, 44 per cent (12) are improved somewhat though not notably, 26 per cent (7) are as before, 11 per cent (3) are somewhat worse and 1 (4 per cent) died of causes unrelated to the arthritis. Hence the prognosis for a spontaneous cure or one induced by the remedies noted herein is only fair. Obviously the disease can be persistent, but if these experiences are characteristic, patients are more likely to become somewhat better than somewhat worse. There appears to be little or no tendency for attacks to lengthen and become confluent, that is, chronic, in a given joint. The disease is a great nuisance to many, a notable handicap to some. But despite the thousands of attacks suffered during a grand total of at least three hundred and seven years of illness (two hundred and forty-two years prior to plus sixty-five years since admission), not a single joint has been crippled permanently.

The Mayo Clinic



# COMPARATIVE STUDY OF ANALGESIC EFFECT OF MORPHINE SULFATE AND MONOACETYLMORPHINE

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A comparative study has been made of the analgesic effects on human beings of morphine sulfate and one of its derivatives, monoacetylmorphine<sup>1</sup> Twenty-four normal males, ranging in age from 17 to 25 years, were used as test subjects in the experiments Pain was produced by means of heat stimulation of the skin of the forehead by means of a modified Hardy-Wolff<sup>2</sup> cutaneous heat radiation apparatus Two components of the pain experience were studied first, the threshold of perception of pain, and, second, the threshold of reaction to pain The accuracy of the method had been established previously by control observations on the variations in sensitivity to pain in 200 normal subjects<sup>3</sup> The measure of the threshold of pain perception was taken to be the lowest strength of stimulus necessary to cause a sharp prick or piercing jab following a sensation of diffuse, burning heat The threshold of pain reaction was taken to be the lowest measurable stimulus needed to cause wincing (observed as a beginning contraction of the muscles of the outer canthus of the eye)

In the original control study it had been found that for subjects on whom repeated observations were made the error inherent in the estimation of pain perception was not more than  $\pm 3$  per cent, while the error for pain reaction showed indi-

vidual variations of from  $\pm 5$  to  $\pm 8$  per cent The purpose of the present study was to determine the relative effectiveness of morphine sulfate and monoacetylmorphine in modifying the perception of pain and the reaction to it A further study of the analgesic effects of monoacetylmorphine was made with a group of 13 normal subjects, a compression method resulting in muscular ischemia being used for the production of pain Throughout all the studies careful observations were made on the side reactions associated with the administration of the two drugs

## METHOD

*A Cutaneous Pain Caused by Heat Radiation—* The source of the pain stimulus was a 1,000 watt Mazda lamp The light from the lamp was focused by two 4 inch (10.2 cm) plano convex lenses through a 2.5 by 2.5 cm aperture onto a blackened area in the mid-forehead Each exposure to the heat stimulus was maintained for exactly three seconds by a shutter operated by a telechron motor The intensity of the stimulus was varied uniformly by a wire rheostat The amount of heat used was measured directly by a radiometer and a potentiometer, and the results were expressed in absolute end point values of gram calories per second per square centimeter of skin surface Each subject was tested under standard conditions and on two different occasions, in order to familiarize him with the test and to establish his normal thresholds for perception of and reaction to pain A description of the end point for perception of pain was elicited by a neutral question technic, so that any error of interpretation due to suggestion might be avoided After the subjective end point for pain was established, the objective measure of the end point of reaction to pain was taken Both end points of sensitivity to pain were again determined for each subject immediately before the administration of the drug to be tested Observations on the drug's effect were made at half-hour intervals for the next four hours, at the same time, questions were asked and notations made as to any resultant side reactions

Each drug was administered subcutaneously, and its dose was standardized as follows morphine sulfate, 0.24 mg, and monoacetylmorphine hydrochloride, 0.06 mg per kilogram of body weight With this ratio, one-

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1 Dr Nathan B Eddy, of the National Institute of Health, Bethesda, Md, furnished an adequate supply of this drug for experimental purposes

2 Hardy, J D, Wolff, H G, and Goodell, H Studies on Pain A New Method for Measuring Pain Threshold, Observations on Spatial Summation of Pain, J Clin Investigation 19 649-657, 1940

3 Chapman, W P, and Jones, C M Variations in Cutaneous and Visceral Pain Sensitivity in Normal Subjects, J Clin Investigation 23 81-91, 1944



fourth as much monoacetylmorphine as morphine sulfate<sup>4</sup> was used

Preparations of the drugs for subcutaneous use were made as follows. Morphine sulfate was prepared as an aqueous solution containing 168 mg per cubic centimeter of distilled water, and monoacetylmorphine hydrochloride, as an aqueous solution containing 42 mg per cubic centimeter of distilled water

Originally each solution was sterilized by being passed through a Seitz filter. The filtered solutions were then placed in boron glass containers (army vaccine type) and kept at room temperature. At the end of sixty days it was found that the analgesic value of the solution of monoacetylmorphine had diminished to a point at which no definite effect could be demonstrated, whereas no apparent change had occurred in the solution of morphine sulfate. Because of this apparent deterioration, the results of all experiments up to this point were discarded. Subsequently, the solution of each drug was sterilized by boiling, at first for fifteen minutes and later for five minutes. In this communication the only results reported are those which followed the use of the freshly prepared solutions, from which apparently full therapeutic results were obtained

Although no definite explanation can be given for the apparent deterioration of the solutions of monoacetylmorphine, some observations may provide a clue. Determinations of  $p_H$  were made with the electropotentiometer on the filtered aqueous solutions which had been kept for sixty days at room temperature, as well as on the freshly prepared solutions. For the former solutions readings of  $p_H$  as low as 2.5 were obtained, while for the latter the values for the  $p_H$  were in the vicinity of 5. Further studies are in progress to determine the stability of such solutions under varying conditions

*B Pain Due to Muscular Ischemia*—Severe aching pain of the forearm and hand was produced by voluntary, uniform, periodic contraction of the hand under conditions of complete vascular occlusion. The subject was examined in the horizontal position with a sphygmomanometer cuff on each arm, and readings of the blood pressure were recorded at intervals. The cuff on the left arm was inflated and maintained at a pressure of 200 mm of mercury throughout the experiment, the circulation in the portion of the arm distal to the cuff being thus completely occluded. Basal blood pressure readings were taken on the right arm over a preliminary five minute period. The subject was then asked to contract his left hand and forearm at intervals of one second for given periods during a total elapsed time of six hundred seconds. Readings of the blood pressure (right arm) were taken at the end of thirty and sixty seconds, and thereafter at one minute intervals during the ten minute test period and for five additional minutes after the pressure on the left arm was released. Since voluntary muscular contractions could not be continued for more than ninety to one hundred and twenty seconds because of fatigue and pain, tests for the effects of contraction were repeated at the end of

two hundred seconds and, again, at the end of four hundred seconds of elapsed time. The number of muscular contractions for each period was charted. During the tests, the examiner made periodic attempts to estimate the severity of pain experienced in the left arm by asking "Is the pain which is now beginning more severe or less severe than, or the same as, that just experienced?"

It is obvious that this method of production of pain, a modification of the procedure standardized by Alam and Smirk,<sup>5</sup> is less accurate than that used in the production of cutaneous pain by measured amounts of heat, but it was thought that the results were of interest for purposes of comparison

After control observations had been completed, the entire test was repeated after the subcutaneous administration of monoacetylmorphine, in the same dose as in the preceding experiments. The results of the tests, that is, the number of contractions performed and the pain experienced by individual subjects, with the drug were compared with the results without the drugs

## RESULTS

*A Cutaneous Pain Caused by Heat Radiation—Morphine Sulfate* The effects of this drug on the threshold of perception of cutaneous pain over a four hour period are shown graphically in table 1. At the end of one-half hour the average elevation of threshold over the basal, or initial, level was approximately 10 per cent. For all the patients the individual range varied from zero to 35 per cent. At the end of one hour the average elevation was 17 per cent, with a range of from zero to 49 per cent in individual subjects. The greatest elevation of threshold was obtained at the end of one and one-half hours, with an average of 20 per cent and an individual variation of from zero to 56 per cent. Thereafter, the analgesic effect diminished, with an average decrease at the end of two hours to a level 16 per cent above the control figure. At the end of two and one-half hours the average elevation above the initial threshold was 11 per cent, at the end of three hours, 17 per cent, at the end of three and a half hours, 11 per cent, and at the final observation, made four hours after the administration of the drug, 10 per cent

Although the measurable effects of the drug varied considerably in individual subjects, only 2 failed to show any increase in threshold of pain perception throughout the course of the experiment. (A complete record of the individual values following the use of the drugs is found in table 1.)

As a general rule, the increases in the threshold of reaction to pain paralleled those in the threshold of perception of pain. In about one-fourth the experiments, definite measurements

4 Such a ratio was originally suggested by Dr Nathan B Eddy. According to information received from Dr Lyndon F Small, of the United States Public Health Service, Bethesda, Md, the actual substances used for comparison were morphine sulfate pentahydrate, containing 75.2 per cent of the alkaloid, and monoacetylmorphine hydrochloride, a hydrated salt containing 78.9 per cent of the alkaloid

5 Alam, M, and Smirk, F H. Observations in Man Concerning the Effects of Different Types of Sensory Stimulation upon the Blood Pressure. Clin Sc 3: 253-258, 1938

of the effect of the drug on reaction to pain could not be obtained, because the initial elevation in the threshold of perception of pain would have necessitated the use of a stimulus capable of blistering the skin at, or before, the point of actual reaction to pain was reached. Such a result, obviously, would have invalidated the thresholds both of perception and of reaction to pain in subsequent studies. In the 30 to 40

Monoacetylmorphine. The effects of this drug are also charted in table 1. At the end of one-half hour there was an average increase in the threshold of pain perception of 17 per cent, although, again, the individual variations ranged from zero to 56 per cent. At the end of one hour the average elevation of threshold was 19 per cent, once more with a wide range, from zero to 56 per cent. As with morphine sulfate,

TABLE 1—*Individual Increases\* (Percentile) in Threshold of Pain Perception Following Administration of Morphine Sulfate and Monoacetylmorphine to Twenty-Four Normal Subjects*

Time	Drug †	Subject	Test	30 Min		60 Min		90 Min		120 Min		150 Min		180 Min		210 Min		240 Min	
				MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM
1	A			0	7	0	14	0		0	21	0	7	0	21	0	7	0	0
	B			0	0	0	11	0	7	0	11	0	18	0	7	0	7	0	14
2	A			14	0	0	42	14	21	14	0	21		0		28		28	0
	B				0	42	0	56	28	28	0			28					
3	A			0	14	0	0	0	0	0	0	0	0						
4	A			21		21	14	21	35	21	18	21	14	21	11	21	18	0	0
5	A			7	42	35		21	18	21	11	21		11	11	0	11	0	7
	B				25		11		11		11		11			4			4
6	A				21	14	21	0		0	14	7				0		0	
	B						18												
7	A			0	14	14	14	14	14	14	14		0	7	0	0	0	0	0
	B				25		18		18		14				11		0		0
8	A				25	46	18		18	60	7			60		18	11		4
9	A			0	35	11	21	49	7		0	0	0	35	0		0		0
10	A				0	42	28	25	14	11	14	14	14		14	14	14		7
	B						25		32		11					4			0
11	A			35	28	0	28	0	18										
12	A			7	32	7	35	7	28	4									
	B						28												
13	A			0	14	14	7	0	0	0	0	14		14		0			
14	A			21	0	21	7	21	0	21	0			0	14		35	0	28
	B			0	0	0	14	0	21	0	14			0	14	0	14	0	
15	A			35	7	49	7	49	0	49	0	49		49	0	35	0		7
	B			14	0	14	42	14	42	0		0		7	35		14	7	11
16	A			21	18	21	7		7	21		11	0	11	0	11	0	11	0
	B			0	0	14	21	21	0	14	0			0	0				
17	A			0		0	14	42		14	14	21	21	56			21	42	0
	B			0	14	0	35	0	35	0	35	0	21	0	18	0	14		14
18	A			7		21				7		7				7		7	
	B			0	28	21	28	28		21	28	14		14					
	C			14		14		28		7		7				7		7	
19	A			14	35	14	49	14	35			49	14		14	35	14		
	B			7	7	14	14	21	28	21	28	28		28		28		28	
20	A			21	0	21	0	35		35	4		0		0		0		0
	B			28	7	35	7	35	7	42	21					39			
21	A			14	7	14	7	42	21	42	7			42	7	28	7	42	7
	B				0		4					11		11					11
22	A			0	42	11	28			18	28	11	21	0		0	21		14
23	A			0	56	14	56	21	42	14	28	4	28	4	28		21	4	21
24	A			14	56	42		21	42	7		21	7	11	0	11			11
Average				10	17	17	19	20	19	16	12	11	15	17	11	11	12	10	8
Range				0-35	0-56	0-49	0-56	0-56	0-42	0-60	0-35	0-49	0-49	0-60	0-35	0-39	0-35	0-42	0-28

\* These increases are determined on the basis of a percentile increase over an initial control level, measured in terms of gram calories per second per square centimeter of skin surface.

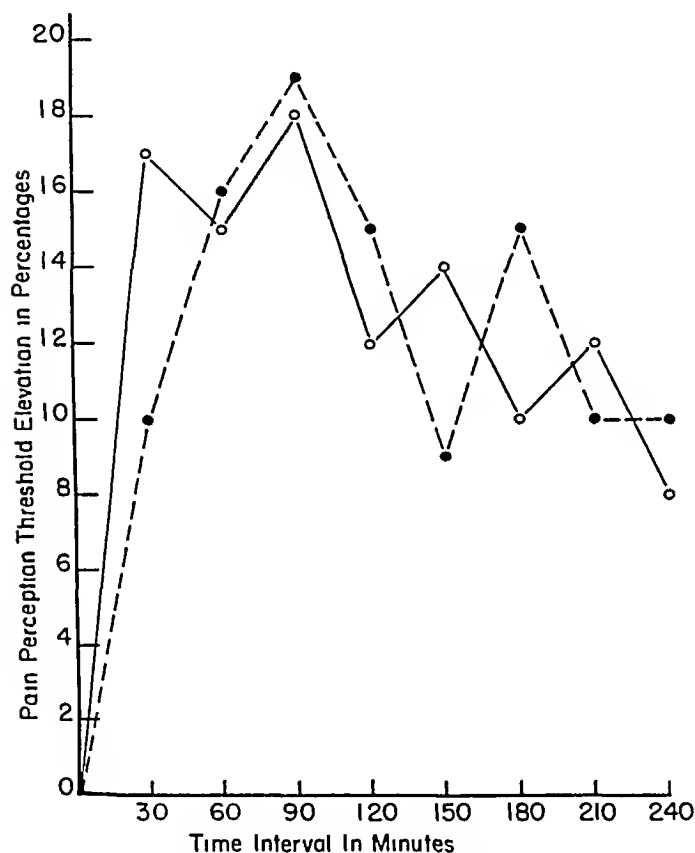
† In this table MS is used to designate morphine sulfate and MAM, monoacetylmorphine.

per cent of subjects whose increase in threshold of reaction to pain did not parallel their increase in threshold of perception of pain, the spread between the two end points ranged from 5 to 49 per cent. In some of these subjects the drug apparently had a relatively greater effect in raising the threshold of reaction to pain than in raising the threshold of perception of pain.

the greatest elevation of the threshold of perception of pain was obtained at the end of one and one-half hours, at which time the average increase for the entire group was 19 per cent, with a range of from zero to 42 per cent above the initial control figures. From this point there was a gradual decrease until, at the end of four hours, the average elevation of threshold was

only 8 per cent. In spite of the wide individual variations, there was absence of an appreciable response to the use of monoacetylmorphine in 1 subject only—subject 3, who was 1 of the 2 subjects who had shown a similar lack of response to the use of morphine sulfate.

The same reasons that made accurate measurement of reaction to pain impossible in the tests with morphine sulfate applied to experiments with monoacetylmorphine. In general, however, no greater increases in the spread between perception of pain and reaction to pain were noted after the use of the latter drug than after the former.



The curves represent average values obtained in studying a group of 20 normal persons. The time intervals (abscissa) represent the number of minutes after the subcutaneous administration of a standard dose of morphine sulfate (broken line) or of monoacetylmorphine hydrochloride (solid line). Ordinate values represent the percentage increases in threshold of pain perception above the initial control figure determined for each subject and expressed as zero.

Comparison of the average curves representing the threshold-raising effects of the two drugs (chart 1) indicates a slight, if any, difference between them. Apparently, the given dose of morphine sulfate (0.24 mg per kilogram of body weight) consistently had a slightly greater analgesic property than freshly prepared aqueous solutions of monoacetylmorphine in doses of one-fourth the amount by weight. It should be pointed out, however, that the difference was not greatly in excess of the error inherent in the method employed.

*B Pain Due to Muscular Ischemia*—In the 13 subjects tested by the method described, severe aching pain in the forearm was produced consistently. This pain was continuous throughout the experiment and increased in intensity after each interval of muscular contraction. The blood pressure readings during the periods in which pain was produced were all elevated. The average increase over the normal systolic pressure was 23 per cent, and that over the normal diastolic pressure, 28 per cent. Detailed readings of the blood pressure with individual variations are shown in table 2.

From the results of the experiments on cutaneous pain due to heat radiation it was obvious that an appreciable analgesic effect of monoacetylmorphine could be expected within thirty to sixty minutes after administration of the drug. Accordingly, forty-five minutes after the injection its effects were measured by repetition of the entire test. Twelve of the 13 subjects noted that, although pain was still present, its intensity was distinctly diminished throughout the period during which vascular occlusion was maintained. The accuracy of this observation was confirmed by the absence of any motor withdrawal or struggling, which had been present uniformly during the control experiment. In spite of this definite diminution of pain following the use of the drug, the elevation of blood pressure during the production of pain did not differ appreciably from that previously noted—the average maximum elevation of systolic pressure being 23 per cent for the entire group and the maximum increase in diastolic pressure being 27 per cent. Another interesting point was the subjective impression obtained by practically all the subjects that the test performed after the administration of monoacetylmorphine covered a much shorter period than the initial test. When asked to state specifically how the time taken by the two tests compared, the subjects answered that the experiment following the drug was one-fourth to one-half as long as the control experiment. Certain subjects described the pain as being sharply localized in the middle of the forearm, as compared with its presence over the entire forearm, and sometimes the hand as well, when no drug was administered. As had been noted in the tests on cutaneous pain due to heat radiation the 1 subject who failed to respond to the administration of either morphine sulfate or monoacetylmorphine again failed in the muscular ischemia test to demonstrate any subjective or objective change in sensitivity to pain following the injection of monoacetylmorphine. In over half the subjects, the total number of muscular contractions of the hand and fore-

arm during the period of production of pain was materially increased after the administration of the drug as compared with the number recorded in the control experiments

*Side Reactions to Drugs* (table 3) —Almost without exception, during the course of the

of 24 subjects After the injection of monoacetylmorphine, only 1 subject had vomiting, and only 7 complained of nausea Vomiting was precipitated apparently in practically every instance by the subject's attempt to walk The other side reactions noted after the administration of mor-

TABLE 2—Results of the Arm Ischemia Test Before and After Use of Monoacetylmorphine

Subject Number	Number of Contractions						Blood Pressure Before Pain	Changes in Blood Pressure			
	First Period		Second Period		Third Period			Percentile Systolic Rise		Percentile Diastolic Rise	
	Before Drug	After Drug	Before Drug	After Drug	Before Drug	After Drug		Before Drug	After Drug	Before Drug	After Drug
1	65	105	20	25	5	—	110/75	30	24	32	29
2	100	120	8	7	3	3	105/60	26	32	29	30
3	59	40	5	12	0	6	125/75	22	20	24	23
4	48	40	4	30	0	30	120/85	24	16	29	26
5	76	135	40	11	8	0	115/75	14	20	31	25
6	114	140	15	20	12	15	110/60	23	23	40	40
7	72	115	40	34	23	42	120/60	22	23	30	30
8	60	85	16	17	12		115/70	35	28	30	29
9	80	100	20	35	35		125/70	24	29	32	30
10	88		30	55		61	110/70	27	23	30	27
11	130	178	21	65	16	88	120/75	26	20	30	25
12	110	100	60	40	30	20	120/75	13	21	25	18
13	90		100	60	0	0	130/80	14	21	20	20
Average no contractions	84	105	26	36	11	20	Average rise	23	23	28	27

TABLE 3—Side Reactions Following Use of Morphine Sulfate and Monoacetylmorphine

Subject No	Nausea		Vomiting		Depression		Elation		Itching		Pallor		Sweating		Sleepiness		Thirst		Dizziness	
	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM	MS	MAM
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	+	—
2	+	—	+	—	+	—	—	—	+	+	+	+	—	—	+	—	+	+	+	—
3	+	—	+	—	+	—	—	—	+	+	+	+	—	—	+	—	+	+	+	—
4	+	+	+	—	+	—	—	+	+	+	+	+	+	+	+	+	+	—	+	—
5	+	—	+	—	+	—	—	—	+	+	+	+	+	—	+	—	+	—	+	—
6	+	+	+	—	+	—	—	+	—	—	++	+	+	—	—	+	—	+	+	—
7	+	—	+	—	—	—	—	—	—	+	—	—	—	—	—	+	—	+	+	—
8	+	+	+	+	+	—	—	—	—	+	+	+	+	+	—	+	+	+	+	—
9	+	+	+	—	+	—	—	+	+	—	+	+	+	—	+	+	—	—	—	—
10	+	—	+	—	+	—	—	—	+	—	+	+	+	—	+	+	+	—	+	—
11	+	—	—	—	+	—	—	+	+	—	+	+	+	—	+	—	+	—	+	—
12	—	—	—	—	—	—	+	+	+	+	+	+	—	—	—	+	—	—	—	—
13	—	—	—	—	—	—	—	+	+	+	+	+	+	—	—	+	—	+	+	—
14	+	+	+	—	+	—	—	—	+	+	+	—	+	—	—	+	—	+	+	—
15	+	—	+	—	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	—
16	+	—	+	—	+	—	—	—	+	—	+	+	+	—	—	+	—	+	+	—
17	+	+	+	—	—	—	—	—	—	+	—	—	+	—	—	+	—	—	—	—
18	+	—	+	—	+	—	+	++	+	—	+	+	+	—	—	+	—	+	+	—
19	+	—	+	—	—	—	—	—	+	+	+	—	—	—	—	+	—	—	—	—
20	+	—	+	—	—	—	—	—	+	—	—	—	—	—	+	—	+	—	—	—
21	+	—	+	—	—	—	—	—	+	—	+	—	—	—	+	+	+	+	+	—
22	+	—	+	—	+	+	—	—	+	+	+	+	+	—	+	+	+	—	+	+
23	+	+	+	—	—	—	—	—	—	+	+	+	+	+	+	+	+	—	+	—
24	+	—	+	—	—	—	—	—	+	+	+	+	—	—	+	+	—	+	+	+
Total subjects	21	7	20	1	14	1	2	8	19	12	22	17	15	4	23	10	23	5	19	4

\* MS indicates morphine sulfate MAM, monoacetylmorphine +, presence of side reaction, and — absence of side reaction

experiments it was noted that the side reactions associated with the use of monoacetylmorphine were less striking than those observed after the injection of morphine sulfate After injection of the latter drug, the most disagreeable reaction was nausea and vomiting, which occurred in 21

phine sulfate, in their order of frequency, were thirst, sleepiness, pallor, dizziness, itching and sweating, and in 1 instance a state of euphoria After the injection of monoacetylmorphine, dizziness was only occasionally observed, being much less apparent than that resulting from morphine

sulfate, pallor and sweating, though experienced, were much less intense, itching (generalized or localized to the nose) was present in about the same degree. A state of euphoria, a striking sense of well-being and mental exhilaration, however, was evident in 8 subjects after administration of monoacetylmorphine, as compared with its presence in 1 subject after injection of morphine sulfate. In general it can be stated that essentially no unpleasant effects were noted after the use of monoacetylmorphine.

#### COMMENT

The results of the studies on cutaneous pain due to heat radiation indicate that in the dose used morphine sulfate was only slightly, if at all, more effective in its analgesic properties than monoacetylmorphine, the difference observed being little greater than the error inherent in the method. The similarity of the two drugs in their effect on elevation of the threshold of pain perception was equally apparent throughout the four hour period of the test, although the dose by weight of morphine sulfate was approximately four times that of monoacetylmorphine. There was little difference, either, in the effect of the two drugs on the threshold of reaction to pain, as measured by the level at which wincing occurred. As previously observed, 2 subjects obtained no analgesic effect whatever from morphine sulfate, and 1 of the 2 subjects also failed to show any demonstrable response to monoacetylmorphine when pain was tested by production of muscular ischemia.

The results of our experiments following the use of morphine sulfate are of interest as compared with the conclusions of Wolff and his collaborators,<sup>6</sup> who used essentially the same dose of the drug. The shape of the curve, indicating a rise in the threshold of pain perception after the administration of morphine (chart), was similar to that obtained by Wolff, but his maximum percental increase was much greater than ours. This discrepancy may be due to a difference in the quality of the sensation which was taken as the beginning of pain perception by the two laboratories. Slaughter,<sup>7</sup> in similar studies with morphine sulfate, obtained changes of the same magnitude of elevation of threshold, with regard to maximum effect and duration of action, as those we obtained.

6 Wolff, H. G., Hardy, J. D., and Goodell, H. Studies on Pain Measurement of the Effect of Morphine, Codeine, and Other Opiates on the Pain Threshold and an Analysis of Their Relation to the Pain Experience, *J. Clin. Investigation* **19**: 659-680, 1940. Hardy and associates.<sup>2</sup>

7 Slaughter, D. Personal communication to the authors.

The clinical significance of the magnitude of the elevation of the threshold of pain perception produced by the use of these two drugs is not clearly understood. It is of interest to note that in current studies being made on the effect of inhalation of nitrous oxide on perception of pain, a subject who had shown an elevation in the threshold of pain perception of 18 per cent after the use of morphine sulfate and of monoacetylmorphine, in the doses employed in this study, had an elevation of 20 per cent after the inhalation of a 50 per cent mixture of nitrous oxide and oxygen. Shortly after this change in threshold following the inhalation of nitrous oxide had been recorded, the subject lost consciousness. For a proper evaluation of this result, it is to be recalled that mixtures containing nitrous oxide in 50 per cent concentration are used routinely for relief of labor pains, a fact which offers indirect evidence of the clinical significance to be attached to the degree of elevation of the threshold of pain following the use of the analgesic drugs employed in the present study.

The striking reduction in pain resulting from muscular contraction in the presence of complete vascular occlusion produced by the use of monoacetylmorphine is in entire agreement with the observations on pain produced by heat radiation. An important difference in the types of pain produced by the two methods deserves comment, however. The pain produced by muscular contraction in the presence of muscular ischemia is a sustained type, more comparable to pain observed clinically than that produced by single, short periods of cutaneous stimulation by intense heat. In the experiments on muscular ischemia it was frequently observed that the use of monoacetylmorphine permitted the subject to contract his fist for longer periods than was previously possible without the use of the drug. Since in this experiment both pain and fatigue contribute to the subject's inability to perform continued muscular contractions, it is readily conceivable that the administration of monoacetylmorphine might, in addition to its analgesic effect, appreciably prolong the ability to continue muscular effort. Such an effect would be of extreme importance in instances in which it is necessary to move wounded or traumatized patients over great distances.

A further suggestion that the use of monoacetylmorphine may be preferable to that of morphine sulfate with ambulatory patients suffering from painful lesions is to be found in the fact that with the former drug not only were few important side reactions encountered but a state of moderate euphoria was frequently associated with its analgesic action. The stimu-

lating effect might be a deciding factor in enabling the patient voluntarily to cooperate in his mobilization. On the other hand, the very absence of side effects makes the possibility of addiction to monoacetylmorphine greater than that to morphine sulfate, and this fact is emphasized. Although studies on the possible deterioration of monoacetylmorphine in aqueous solution are not conclusive, our observations suggest the need for careful study of the physical properties of the drug under varying conditions of temperature, solution and the like.

#### SUMMARY

1 Comparative studies on a group of 24 normal subjects on the analgesic effects of morphine sulfate and of monoacetylmorphine on cutaneous pain produced by the heat radiation method of Wolff and Hardy and on muscular pain produced by muscular exercise under conditions of complete vascular occlusion of an extremity (muscular ischemia) indicate that a given dose of

monoacetylmorphine is about four times as effective as a similar dose of morphine sulfate in control of pain, as regards both the maximum elevation of threshold obtained and the duration of its action.

2 The side reactions incident to the use of monoacetylmorphine are distinctly less than those associated with the administration of morphine sulfate. This is particularly true with regard to the occurrence of nausea and vomiting.

3 The use of monoacetylmorphine, in addition to its analgesic effect, appears to permit increased voluntary muscular effort in the presence of severe pain, as evidenced by the experiments with muscular ischemia.

4 Notable individual variations occurred in the responses to each of the drugs employed. Two subjects obtained no measurable analgesic effect from morphine sulfate and relatively little from monoacetylmorphine.

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# POSTOPERATIVE THROMBOCYTOSIS

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Among experimental and clinical measures which are reported to raise the platelet count, surgical procedures, particularly splenectomy, have attracted much attention. This phenomenon is of interest for at least two reasons. First, the rise in the platelet count is more difficult to rationalize than many of the other thrombocytoses, such as those related to primary augmentation of the function of the bone marrow, second, the association of platelets with the clotting process has led to the loosely formulated belief that their increase after a surgical operation is connected with the occurrence of postoperative thrombosis.

The first extensive clinical investigation of this subject to be reported was that of Hueck<sup>1</sup> in 1925, who studied 100 varied surgical patients and found a brief fall in the platelet count postoperatively, followed by a rise to as much as three times the normal preoperative level. Hueck found the rise to begin at about the seventh postoperative day and the count to return to the preoperative level by two weeks after operation. Dawbarn, Earlam and Evans<sup>2</sup> made one of the most comprehensive studies reported in English. Fifty patients were found to show a substantial rise in platelets after operation, the maximal values being reached on the tenth postoperative day. The authors were impressed by a general correlation between the extent of the operation and the degree of increase in platelets and suggested that the elevation might be related to the reabsorption of necrotic tissue.

A number of corroborative papers have since appeared, among them those of Normann,<sup>3</sup> König<sup>4</sup> and Gradwohl and Hiller.<sup>5</sup> A single

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1 Hueck. Blutplättchenveränderungen nach Operationen, *München med Wchnschr* **73** 173, 1925.

2 Dawbarn, R. T., Earlam, F., and Evans, W. H. Relation of Blood Platelets to Thrombosis After Parturition and Pregnancy, *J Path & Bact* **31** 833, 1928.

3 Normann, E. Wie verhalten sich die Thrombocyten nach operative behandelten Krankheitsfällen und die der Entstehung postoperative Thrombose? *Deutsche Ztschr f Chir* **212**:166, 1928.

study of the platelet volume postoperatively<sup>6</sup> indicated that there is actually more circulating platelet material and answered the question as to whether the rise represents merely an increase in the amount of platelet fragmentation. Experimental animals have yielded approximately the same results as human patients. Several investigators have demonstrated a moderate but significant rise in the rabbit.<sup>7</sup>

The observation of a postoperative and post-traumatic rise in the platelet count has not gone unchallenged. Allen<sup>8</sup> in 1927 was unable to discover any variation from normal in 12 patients followed postoperatively, details of counting technic and length of follow-up were not presented. Fisher<sup>9</sup> likewise reported no significant changes in the counts of 6 patients after operation, but he pointed out that these persons were followed for only six days each. The most formidable negative report is a recent one by Potts and Pearl.<sup>10</sup> In a group of 52 patients who had had major operations, they found only minimal changes consisting in an average rise of 9 per cent above the preoperative level of platelets.

The thrombocytosis occurring after splenectomy is accepted more universally than that re-

4 König, W. Experimentelle Untersuchungen über die Entstehung der Thrombose, *Arch f klin Chir* **171** 447, 1932.

5 Gradwohl, R., and Hiller, S. T. Blood Platelet Count in Postoperative Thrombosis, *J Mississippi M A* **31** 392, 1934.

6 Evans, W. I., and Fowler, W. M. Effect of Splenectomy and Other Operations on Platelets as Determined Volumetrically, *Proc Soc Exper Biol & Med* **32** 512, 1934.

7 Bachman, E. L., and Hultgren, G. Influence de l'intervention chirurgicale sur la teneur du sang en thrombocytes, *Compt rend Soc de biol* **94** 942, 1926. Liles, R. T. Blood Platelets in Rabbits Following Splenectomy and Transplantation of Spleen, *Proc Soc Exper Biol & Med* **23** 489, 1926. Steiner, P. E., and Gunn, F. D. Effect of Splenectomy and Other Surgical Procedures upon Circulating Blood Platelets, *ibid* **28** 1088, 1931.

8 Allen, E. V. Changes in the Blood Following Operation, *Arch Surg* **15** 254 (Aug) 1927.

9 Fisher, L. C. Platelet Count After Splenectomy and Other Operations, *Proc Soc Exper Biol & Med* **29** 316, 1931.

10 Potts, W. J., and Pearl, E. Platelet Count and Coagulation Time of Plasma and Whole Blood Postoperatively, *Surg, Gynec & Obst* **73** 492, 1941.

ported to follow other types of operation. The highest platelet counts encountered are those for splenectomized patients,<sup>11</sup> and it is recognized that these high levels may be maintained for many months following operation.<sup>12</sup> The rise occurring after splenectomy is found in a variety of diseases involving the spleen, as well as after removal of the normal traumatically ruptured spleen.<sup>13</sup> While the cause of the thrombocytosis which occurs after other operations is poorly understood, it is believed that after splenectomy increases in platelets are due, at least in part, to the removal of the normal thrombolytic activity of that portion of the reticuloendothelial system.<sup>13b</sup> Bedson<sup>14</sup> offers some experimental corroboration of this view.

Although the occurrence of a postoperative thrombocytosis seems fairly well established, many of the confirmatory studies are based on varied and poorly controlled methods of counting. In addition, as previously mentioned, there are several negative reports in the literature. Therefore, it is worth while to report some observations on a group of surgical patients with a simple direct venous platelet-counting method, the advantages of which have been discussed by Tocantins.<sup>15</sup>

#### METHODS

After several different counting methods had been tried, a method essentially that of Nygaard<sup>16</sup> was found most satisfactory. This is a direct plasma platelet count which has many of the advantages of Thomsen's<sup>17</sup> technic but escapes the disadvantage of requiring a hematocrit determination.

The materials required include a 10 cc syringe calibrated in single cubic centimeters, 50 cc

centrifuge tubes, a sterile 1:1 per cent solution of sodium oxalate, an unsterile refrigerated 1:1 per cent solution of sodium oxalate, and uncalibrated capillary pipets.

Through a 20 gage needle, a 10 cc syringe is carefully filled with sterile 1:1 per cent sodium oxalate solution exactly to the 9 cc mark. A venipuncture is done with minimal trauma, and with light or no stasis. If stasis is used, the tourniquet should be released as soon as the vein is entered, and five seconds should elapse before the blood is withdrawn. Blood is then removed until exactly 1 cc has been taken—i.e., the plunger of the syringe is at the 10 cc mark. The resultant blood-oxalate mixture is placed in a clean dry 50 cc centrifuge tube, and with the same syringe and needle an additional 30 cc of 1:1 per cent sodium oxalate solution, which need not be sterile, is transferred to the centrifuge tube, so as to make a resultant 1:40 dilution of the original 1 cc of blood. This is now mixed by inverting, and then the centrifuge tube is capped to prevent evaporation and is placed upright in a cool place to await sedimentation of the red and white cells. When a narrow but definite bank of clear plasma-oxalate has appeared at the top of the fluid (usually one to two hours), a small amount of this overlying oxalated plasma is taken up in a clean dry capillary pipet and placed in both sides of a counting chamber.<sup>18</sup> After at least ten minutes is allowed for the platelets to settle, the count is made with the high dry lens (400 diameters) under reduced light. The field seen is almost free of red and white cells and contains chiefly platelets. These appear typically as small (2 to 5 micron), sharply defined bodies, which are either highly refractile or dark, depending on the clearness of focus. They are usually globular but may present long processes or irregular shapes, as noted by many observers.<sup>19</sup> Ten small squares are counted for each determination, five on each side of the chamber, as for a red cell count, and the result multiplied by the dilution factor of 1,000 (blood dilution 1:40, 0.04 cu mm of blood counted in ten small squares) to give the number of platelets per cubic millimeter of whole blood.

In Thomsen's method, the error made by counting platelets in virtually cell-free oxalated plasma and then calculating them for whole blood is a considerable one, which requires correction by the hematocrit reading. With the

11 Tocantins, L. M. The Mammalian Blood Platelet in Health and Disease, *Medicine* **17** 155, 1938.

12 Galloway, J. F. Blood Platelets After Splenectomy, *Lancet* **2** 1235, 1931.

13 (a) Woolstein, M., and Kreidel, K. Blood Picture After Splenectomy in Children, *Am J Dis Child* **51** 765 (April) 1936. (b) Krumbhaar, E. B. Changes Produced in Blood Picture by Removal of Normal Mammalian Spleen, *Am J M Sc* **184** 215, 1932. (c) Evans, W. H. Blood Changes After Splenectomy, *J Path & Bact* **31** 815, 1928.

14 Bedson, S. P. Effect of Splenectomy on Experimental Purpura, *Lancet* **2** 1117, 1924.

15 Tocantins, L. M. Technical Methods for the Study of Blood Platelets, *Arch Path* **23** 850 (June) 1937.

16 Nygaard, K. K. Direct Method of Counting Platelets in Oxalated Plasma, *Proc Staff Meet, Mayo Clin* **8** 365, 1933.

17 Thomsen, O. A Method for the Direct Count of Blood Plates in the Blood, *Acta med Scandinav* **53** 507, 1920.

18 Levy-Hausser dark line chambers were used throughout.

19 Ferguson, J. H. Observations on the Alterations of Blood Platelets as a Factor in the Coagulation of the Blood, *Am J Physiol* **108** 670, 1934.

high dilution of blood employed in the present method, however, this error becomes negligible Nygaard<sup>16</sup> calculates that even with a hematocrit reading of 75 per cent only 3.75 per cent need be subtracted from the platelet count made in a final blood-oxalate dilution of 1:20. With a 1:40 dilution, as was employed in the counts to be reported, the error is much smaller.

The presence of bacteria, which resemble platelets in the counting chamber and may therefore artificially raise the count, is avoided by employing only diluting fluid that is either sterile or refrigerated. Repeated blank counts on the unsterile diluting fluid alone have never shown the presence of more than 5 to 10 platelet-like bodies in the total area examined.

Still another factor must be considered in a method which depends on differential sedimentation of the red cells and the platelets—the magni-

sible source of error. Wright<sup>20</sup> showed that the magnitude of this error could be considerable and that the degree of loss of platelets from solutions by this route varied inversely with the concentration of anticoagulant used. In an attempt to evaluate this factor, preparations exactly like those used for counting were centrifuged at 1,600 revolutions per minute for one minute and samples of the platelet-rich supernatant were placed in each of two test tubes, one paraffined and the other plain. These tubes were slowly rotated, and platelet counts were made on samples from them at short intervals. It was found for both a normal subject and a postoperative patient that no significant drop in the number of platelets occurred during the first two hours and that there was no appreciable difference in this period between the concentration of platelets in the paraffined and that in the nonparaffined

*Preoperative and Maximum Postoperative Platelet Counts in a Sample Group of Patients*

Patient	Name	Sex	Age	Operation	Last Preoperative Count Platelets per C Mm	Maximum Postoperative Count Platelets per C Mm	Post-operative Day (Maximum Count)	Per Cent Rise
1	J. C.	M	83	Hip pinning	314,000	398,000	11	25
3	I. V.	M	23	Laminectomy	387,000	817,000	9	110
4	M. V.	F	43	Herniorrhaphy	277,000	605,000	6	118
5	C. M.	M	71	Nephrectomy	522,000	841,000	16	61
6	A. M.	M	74	Prostatectomy	241,000	384,000	8	59
7	F. G.	M	35	Mid thigh amputation	293,000	562,000	11	91
11	E. M.	M	24	Laparotomy	464,000	608,000	6	28
12	G. P.	F	56	Laparotomy	498,000	711,000	6	42
13	M. B.	F	66	Resection of colon	464,000	538,000	13	16
14	A. K.	F	55	Cholecystectomy	422,000	671,000	20	59
34	J. W.	M	54	Mid thigh amputation	382,000	654,000	12	72
39	S. H.	M	45	Herniorrhaphy	325,000	397,000	10	22
10	C. M.	M	42	Splenectomy	113,000	1,800,000	11	1,470
18	W. T.	M	23	Splenectomy	348,000	1,489,000	11	328

tude of the factor of loss of platelets from the overlying suspension by sedimentation and by adhesiveness to the glass walls of the container. Trials were made of the suspension stability of platelets in preparations identical with those used for the counts reported. Blood was taken from 2 ostensibly normal persons and from 2 postoperative patients with elevated platelet counts. Serial counts were made on each of these specimens over a period of twenty-four hours, samples being aspirated from three different levels of each preparation (top, middle and bottom of the clear overlying layer) at the end of each time interval. These platelet suspensions were found to be stable for at least six hours, and within this period the counts made on them did not vary significantly with time or region.

Since paraffined tubes were not routinely used, adhesiveness of platelets—chiefly to the glass walls of the container—was another pos-

sible source of error. The disparity between these results and those of Wright is probably ascribable to the much higher concentration of anticoagulant used for the diluting fluid in the present studies, as well as to the use of greatly diluted plasma.

A final test of the method, and the most realistic one, was a series of six sets of duplicate counts made for the same persons at the same time. When blood was withdrawn from each of the two arms and prepared and examined for platelets separately, the average discrepancy in the two counts of each set was only 6 per cent.

#### RESULTS

*1 Normal Counts*—Platelet counts were made for 36 ostensibly normal young persons, including nurses, medical students and patients hos-

<sup>20</sup> Wright, H. P. The Adhesiveness of Blood Platelets in Normal Subjects with Varying Concentrations of Anti-Coagulants, *J. Path. & Bact.* **53**: 255, 1941.

pitalized for functional psychiatric disorders. The average of these counts was 322,000 per cubic millimeter, with a range of from 236,000 to 445,000. It is of interest that the average of these 36 counts is approximately the same as Nygaard's average for a much larger series of normal counts, "about 320,000 per cubic millimeter" <sup>16</sup>

**2 Preoperative Counts**—Preoperative counts were made for 63 varied surgical patients, many of whom were subsequently followed postoperatively. The average for this group was 365,000

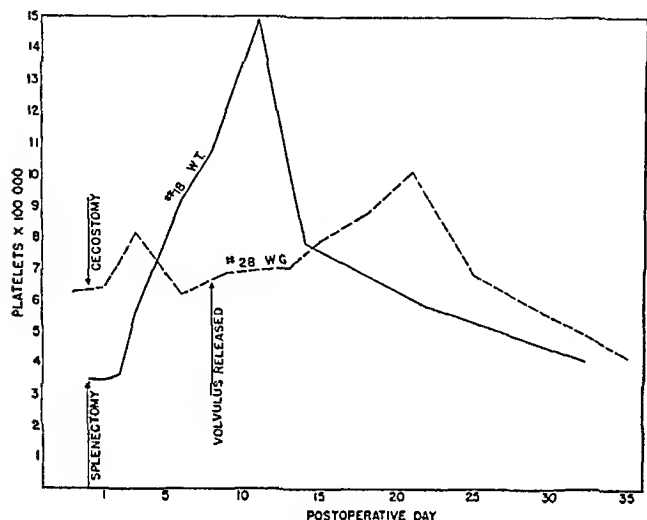


Chart 1—Individual examples of postoperative platelet changes

per cubic millimeter. The difference between this and the normal average, if significant, can perhaps be ascribed to the presence among the preoperative group of chronic infections and other disorders known to elevate the platelet count. Serial counts on alternate days were done preoperatively for a number of these persons for variable periods up to a month without the appearance of any large fluctuations in the preoperative level of platelets.

**3 Postoperative Counts**—Forty-one patients chosen at random were followed postoperatively for periods ranging from eight to thirty-six days. These patients were suffering from various disorders and underwent varied types of operations, including splenectomy. In the table are shown the degree and the time of occurrence of the maximum postoperative rise in a sample group of the subjects followed, since space does not permit detailed presentation of these data for the entire group. The percentage rise is calculated on the basis of the last preoperative count as 100 per cent. For most patients only one preoperative count was done, the remaining ones had no preoperative counts significantly or consistently higher than the final count preceding operation. Charts 1 and 2 show graphically the time rela-

tions and the extent of the changes in platelet level for several of the patients followed. Chart 3 is a graphic summary of the complete data presenting the averaged absolute counts and percentage differences throughout the period that patients were followed. The values for the average platelet count of the normal group and those of the preoperative group are superimposed for comparison in the lower half of chart 3, while in the upper half the percentage values of the average platelet count at the various days are calculated on the basis of the final preoperative count as 100 per cent.

In evaluating the series of postoperative platelet counts, one is faced with a number of complexities. It is clear that there are many factors in surgical procedures beyond the mere operative onslaught, all of which may have a profound effect on the platelet count. These patients presented different disease pictures originally, underwent operations of varying type and extent and lost variable amounts of blood. Some were given transfusions before and after operation and some received sulfonamide compounds as well as other drugs before and after operation. In addition, a number of the patients had various postoperative febrile complications, such as pneumonia, infection of the wound or infection of the urinary tract. These varied factors might be expected to have some effect on the concentration of platelets in the peripheral circulation. At present, however, there is no way of eliminating these variables, which will no doubt be found in any group of surgical patients. Hence one can only neglect them, after calling attention to their presence.

Excluding the 2 splenectomized patients from consideration, 22 of the 39 remaining patients

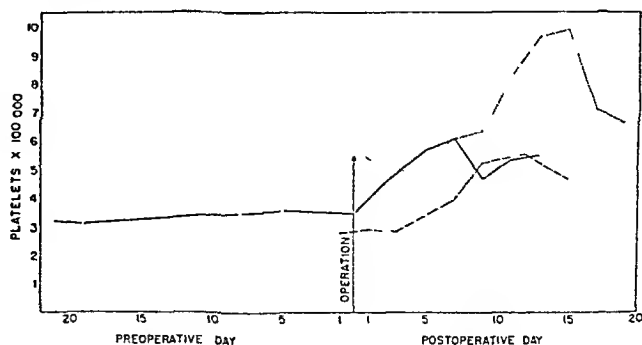


Chart 2—Individual examples of postoperative platelet changes. The line of short dashes represents case 8 (abdominoperineal resection), the solid line, case 15 (sigmoid resection), and the line of longer dashes, case 21 (nephrolithotomy).

had a postoperative rise of platelets amounting to more than twice the standard deviation of the group of preoperative counts (105,000 per cubic millimeter). This degree of increase is taken

conservatively to be significant, although inspection of the individual protocols suggests a greater incidence of significant elevations

In charts 1 and 2 are shown several representative individual platelet responses to operations. Among the most convincing are those of patients who had two separate operations, each succeeded by a distinct rise in the platelet count. Case 28 exemplifies this. Cecostomy was followed by an immediate and rapidly receding increment in the platelet count. A volvulus then developed, requiring immediate operation on the fourteenth day after cecostomy, when the platelet count had already returned to its preoperative level. After this incident, a higher, more sustained elevation occurred, with a peak at slightly over 1,000,000 per cubic millimeter. Thirty-five days postoperatively the count had reached an approximately normal level. Case 21 is charted because it is a typical example of the postoperative change in the platelet count, with its peak between the

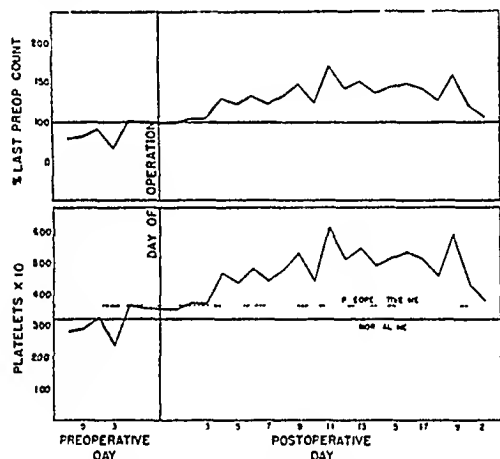


Chart 3—Average absolute and percentage rise in the platelet count of 41 patients following operation

tenth and the fifteenth day. Case 15 demonstrates the relative constancy of serial preoperative counts for these patients, which was noted for most, but not all, of the persons followed. The platelet response in case 18 is rather typical of that following splenectomy, as reported by other investigators previously mentioned. Case 8 demonstrates that a substantial rise in platelets may occur postoperatively even though the preoperative level of platelets is already much elevated.

These data support the conclusion that a significant rise in the level of blood platelets occurs postoperatively but that it is a variable one, ranging from 30 per cent to more than 100 per cent above the preoperative level. It seems equally true that this phenomenon is not demonstrable in every case.

The time relations of the maximal rise are likewise variable. The period from the seventh to the twentieth postoperative day includes the

great majority of the individual peaks, and these are most frequent in the interval between the tenth and the fourteenth day inclusive—an observation in substantial agreement with the results of previous investigators. The maximal platelet counts of the subjects in this study, however, occurred anywhere from the day of operation to the twenty-first postoperative day.

#### COMMENT

Postoperative thrombocytosis is difficult of explanation, in part because the rise following operation is so long delayed (eight to fifteen days). The hypothesis generally offered is that it is in some manner dependent on absorption from the wound of necrotic material, exudate, etc., a point of view which is supported by certain experimental observations. König<sup>4</sup> and Zschau,<sup>21</sup> for example, demonstrated a similar rise in platelets after the parenteral administration of isogenous tissue extracts and the implantation of autogenous muscle grafts in animals. Pohle<sup>22</sup> likewise suggested that the periodic postmenstrual rise in platelets in normal women may be due to the absorption of necrotic endometrium. Moreover, Dawbarn, Earlam and Evans<sup>2</sup> explained the increase in platelets during convalescence from pneumonia on the basis of absorption of the resolving exudate. An alternative hypothesis was originally suggested by Hayem<sup>23</sup> that the thrombocytosis is an overcompensatory response to the initial thrombopenia noted both in immediate postoperative periods and during acute infections.

The etiologic significance of postoperative thrombocytosis in the occurrence of clinical thrombosis is a problem which requires much clarification. Platelets are believed to function in blood coagulation by virtue of two fundamental mechanisms: (1) the release of thromboplastin in initiating the plasma clotting process and (2) agglutination, either reversible or irreversible, to each other and to vascular endothelium. These functions are distinctly separated in lower forms, such as *Limulus*,<sup>24</sup> and may be experimentally separated in the mammal by the use of heparin.<sup>25</sup> The importance

21 Zschau, H. Untersuchungen zur Thrombosefrage, *Deutsches Arch f klin Chr* **230** 13, 1931.

22 Pohle, F. J. Blood Platelet Count in Relation to Menstrual Cycle in Normal Women, *Am J M Sc* **197** 40, 1939.

23 Hayem, G. De la crise hematique dans les maladies aiguës à defervescence brusque, *Compt rend Acad sc* **94** 200, 1882.

24 Loeb, L. Amoeboid Movement and Agglutination in Amoebocytes of *Limulus*, *Protoplasma* **2** 572, 1927.

25 Solandt, D. Y., and Best, C. H. Time Relations of Heparin Action on Blood Clotting and Platelet Agglutination, *Lancet* **1** 1942, 1940.

of either or both together (as interdependent events in clotting) in initiating clinical thrombosis has not been assessed, nor is it known whether a tendency toward intravascular clotting by either mechanism is significantly enhanced by the mere presence of a greater number of circulating platelets. In fact, it would seem that, while the clotting of plasma is appreciably slowed by marked reduction in the number of contained platelets, yet even a great increment in their concentration has no effect in the reverse direction of accelerating clotting.<sup>26</sup> The purely agglutinative properties of platelets acquire more interest, however, in the light of the present belief that antemortem thrombi are first formed from agglutinated platelets<sup>27</sup> and that the red portions of the clot are formed only later from all the elements of the circulating blood.

Functional changes in platelets postoperatively have been examined in a number of ways in recent years. The agglutinability of platelets has been found to be enhanced in the presence of clinical thrombosis<sup>28</sup> and postoperatively.<sup>29</sup> The adhesiveness of blood platelets, measured by a simple method, has recently been shown to increase postoperatively, paralleling the postoperative thrombocytosis.<sup>30</sup> A decrease in the resistance of platelets to hypertonic solutions has also been noted in the thrombocytoses occurring after infections and after operations.<sup>31</sup>

Satisfactory empiric evidence that thrombocytosis increases the chances of thrombosis, how-

ever is so far lacking. While peripheral and mesenteric thromboses are not infrequent after splenectomy for splenic anemia,<sup>32</sup> they do not occur so commonly after splenectomy for other conditions, although operations of the latter type are followed by an equally pronounced thrombocytosis.<sup>33</sup> Fatal thromboses have been often reported in the presence of a normal or subnormal platelet count,<sup>34</sup> while there are numerous instances of extremely high counts uncomplicated by evidence of thrombosis.<sup>34b</sup>

Although the series here studied is admittedly small, the data presented seem neither to support clearly nor to argue against the tissue-trauma hypothesis of postoperative thrombocytosis. It is true that inspection of the data shows a rough correlation between the extent of operation and the degree and maintenance of the postoperative elevation. The patients subjected to major abdominal operations involving a good deal of dissection and manipulation clearly showed a greater platelet response than those who were recovering from operations such as subtotal thyroidectomy. In the middle range of surgical procedures, however—the perineal prostatectomies, herniorrhaphies, laparotomies, etc.—the postoperative elevations were variable and seemed not to depend closely on the severity of the operation.

Differential platelet counts were not attempted, but it was noted incidentally that in many cases the average size of the postoperative platelets, as seen in the counting chamber, was reduced, sometimes strikingly so, compared with the same patient's platelets preoperatively. The possible significance of this fact has been discussed by Olef.<sup>35</sup>

In only 1 patient did a serious thromboembolic accident complicate the postoperative course. This occurred in a 72 year old man who was operated on for carcinoma of the rectosigmoid. Three days before operation the platelet count was 1,221,000 per cubic millimeter. It rose to 1,489,000 on the evening of the day of operation and fell to approximately 1,000,000 on the fourth postoperative day. On the fifth day the patient died suddenly of the effects of a

26 Eagle, H. Studies on Blood Coagulation. Role of Prothrombin and of Platelets in the Formation of Thrombi, *J Gen Physiol* **18** 531, 1935. Nygaard, K. K. Hemorrhagic Diseases, St. Louis, C. V. Mosby Company, 1941.

27 Bizzozero, J. Ueber einen neuen Formbestandteil des Blutes und dessen Rolle bei der Thrombose und der Blutgerinnung, *Virchows Arch f path Anat* **90** 261, 1882. Welch, W. H. The Structure of White Thrombi, in *Papers and Addresses*, Baltimore, Johns Hopkins Press, 1920, vol 1, p 47. Shmonoya, T. Studies in Experimental Extracorporeal Thrombosis, *J Exper Med* **46** 18, 1927. Best, C. H., Cowan, C., and Maclean, D. L. Heparin and the Formation of White Thrombi, *J Physiol* **92** 20, 1938.

28 Jurgens, R., and Bach, K. Thromboseneigung in Polycythemia Vera, *Deutsches Arch f klin Med* **176** 626, 1934.

29 Heusser, H. Postoperative Blutveränderungen und ihre Bedeutung für die Entstehung der Thrombose, *Deutsche Ztschr f Chir* **210** 132, 1928. Jurgens, R., and Naumann, W. Klinische und experimentelle Untersuchungen über Funktionen der Blutplättchen, *Deutsches Arch f klin Med* **172** 248, 1932.

30 Wright, H. P. Changes in the Adhesiveness of Blood Platelets Following Parturition and Surgical Operations, *J Path & Bact* **54** 461, 1942.

31 Olef, I. The Rate of Disintegration of Platelets, *J Lab & Clin Med* **22** 128, 1936. König<sup>4</sup>

32 Rosenthal, N. Clinical and Hematological Studies on Banti's Disease, *J A M A* **84** 1887 (June 20) 1925.

33 Patey, P. H., in *Discussion on Postoperative Thrombosis*, *Proc Roy Soc Med* **22** 733, 1929.

34 (a) Bryce, A. G. Splenectomy and Thrombosis, *Lancet* **2** 1423, 1932. (b) Mackay, W. The Blood Platelet Its Clinical Significance, *Quart J Med* **24** 285, 1924. (c) Evans and Fowler<sup>6</sup>

35 Olef, I. The Differential Platelet Count Its Clinical Significance, *Arch Int Med* **57** 1136 (June) 1936.



large pulmonary embolism. Autopsy revealed the presence of large antemortem clots in the periprostatic veins and the inferior vena cava.

In this person two phenomena were observed: a high thrombocyte count and a postoperative thromboembolic accident. Suggestive as they are, however, they offer none but the usual suppositious evidence for the platelet factor in thrombosis. In the first place, the increase in the platelets was not actually postoperative, since the count of 1,221,000 per cubic millimeter was made three days before operation. Furthermore, there were present in this series of studies 4 other platelet levels above 1,000,000 per cubic millimeter, 1 occurring in a preoperative patient with a bleeding gastric ulcer, another occurring on the twenty-first day following cecostomy (chart 1) and the remaining 2 occurring in the

2 splenectomized patients. None of these patients exhibited any clinical evidence of thrombosis or embolism.

#### CONCLUSIONS

1 A substantial postoperative rise in the level of the blood platelets is a phenomenon which occurs commonly, though not without exception.

2 The degree and time of the maximal elevation are variable, although a majority of the patients show the maximal rise between the tenth and the fifteenth postoperative day.

3 No definite correlation between the extent of the operation and the degree of the postoperative rise can be established, although a rough relationship is suggested.

Dr. John S. Lawrence gave encouragement and advice throughout this work.

# ELECTRIC SHOCK THERAPY IN A GENERAL HOSPITAL

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AND NICHOLAS PETER DALLIS, MD

DETROIT

There has been sustained interest in the shock therapies since 1932, when Sakel<sup>1</sup> introduced insulin coma for schizophrenia. Its use for several years was rather empiric, and today it is used only in selected cases. In 1935 Meduna<sup>2</sup> added metrazol convulsive therapy to the treatment of schizophrenia. It was soon found, however, to be most effective for the depressed states, particularly the reactive depressions. It was heralded as a specific for the depressions but was frowned on because of its orthopedic complications and the fears patients expressed toward it.

It is five years since electric shock therapy was introduced by Cerletti and Bini.<sup>3</sup> There are now available a sufficient number of reports on this therapy to permit some definite conclusions. Electric shock has been accepted with considerable enthusiasm, and, although most investigators have been disappointed by their results in the treatment of some psychoses, particularly schizophrenia, it is an almost specific therapy for the depressions.

The purpose of this paper is to review the present status of electric shock therapy and to present an additional 100 cases. We feel that these cases will be of particular interest because most of them deal with mental disease in its incipency, many of the patients having been referred from the offices of general practitioners or of specialists who recognized in their patients the need for psychiatric care. Included, too, are the cases of treated patients who had been under our care for some time in our hospital or our outpatient clinic.

Electric shock therapy has almost completely replaced metrazol convulsive therapy because of certain advantages in its administration, most obvious of which is the absence of apprehension

or panic in the patient, which was commonly encountered with metrazol. In addition to this, the seizure with the electric shock method can be more uniformly produced in a given person than it can with the drug method. Also, the seizure with electric shock is not so severe, and its resulting complications, therefore, are not so frequent.

The apparatus used in electric shock is a compact unit and easily carried. There are several makes available, but all are built on the same plan. Ordinary alternating "house" current of 80 to 150 volts is used, and the strength is set in milliamperes varying from 300 to 650 and flowing for one tenth to eight tenths of a second. We have used 110 volts with the milliamperage between 400 and 450 for three tenths or five tenths of a second in the average case. We produced the desired response in 1 patient with 350 milliamperes for three tenths of a second, and 1 patient required 650 milliamperes for five tenths of a second to produce a convulsive response. Generally speaking, the strength of the current required depends on the size of the patient—the larger the subject the greater the strength required. This is, however, by no means the rule.

There are three types of reaction which may occur. Smith, Hughes and Hastings<sup>4</sup> called these the "missed," the "equivalent" and the "grand mal" reaction. In the missed reaction there is a sudden start with almost immediate consciousness and no recollection of the episode. In the equivalent reaction there is the sudden start but the patient does not regain consciousness for a period of seconds to minutes. There is usually apnea during this period. There may be some spasticity and twitching of the extremities. The patient then rouses slowly during the next ten to fifteen minutes. Some believe this reaction to be equivalent therapeutically to the convulsive, or grand mal, response. We do not believe this to be the case, and we endeavor to produce the grand mal reaction. In the last type, again, is the same start and the patient may im-

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1 Sakel, M. *Neue Behandlungsmethode der Schizophrenia*, Vienna, Moritz Press, 1935.

2 Meduna, L. *New Methods of Medical Treatment of Schizophrenia*, Arch Neurol & Psychiat 35 361 (Feb) 1936.

3 Cerletti, U, and Bini, L. *Un nuovo metodo di shockterapia "l'elettro-shock" (riassunto)*, Boll ed atti d r Acad med di Roma 64 136, 1938.

4 Smith, L. H., Hughes, J., and Hastings, D. W. *First Impressions of Electroshock Treatment*, Pennsylvania M J 44 452, 1941.

mediately go into a generalized epileptiform seizure or there may be a short latent period before the seizure. The seizure lasts between fifteen and sixty seconds. Following this, there is usually a period of apnea, and then the patient begins breathing loudly and moistly. There may be a period of excitement and then confusion for fifteen to thirty minutes.

Prior to giving a patient electric shock therapy it has been our rule to have the family sign a permit, explaining the complications and the dangers associated with the treatment. After this is done, in addition to the routine physical and neurologic examinations and studies of the blood and urine, we make an electrocardiographic tracing and a roentgenogram of the thoracic portion of the spine, anterior and posterior. Electric shock therapy should not be used in the presence of coronary disease or advanced heart disease. The roentgenogram of the spine is to rule out pathologic conditions of the bones. Compression fractures which may occur almost always involve the thoracic area. We avoid sedation as much as possible for twelve hours before treatment. The patient should have no food for two hours before treatment, and artificial dentures and bridgework should be removed.

The contraindications for convulsive therapy, in addition to advanced heart disease and pathologic conditions of the bones, are organic disease of the brain, advanced arteriosclerosis, active tuberculosis and thrombophlebitis. Naturally, there are times when therapy may be indicated even in the presence of one or more of these conditions. Jones and Pleasants<sup>5</sup> have used electric shock for highly agitated patients with dementia paralytica prior to giving them hyperpyrexia. Evans<sup>6</sup> reported the case of a woman with generalized osteoporosis to whom he gave metrazol convulsive therapy. Evans<sup>7</sup> also reported giving electric shock therapy to a 74 year old woman with a complete left bundle branch block without untoward complications.

The number of treatments given varies with the individual case. We have given as few as one treatment and as many as twenty-four. Kay, Smith and Reim<sup>8</sup> reported that they gave 1 pa-

tient sixty-one treatments, and we believe this to be a record high. The average course of treatment for a depression is eight, a manic-depressive psychosis requires about twelve, schizophrenia at least ten and a psychoneurosis between two and six. The treatments are usually given two or three times each week. We have found that this is not frequent enough for the extremely agitated patients with depression or for the highly active manic patients. Therefore, certain patients are given daily treatments for four or five consecutive days and then every other day as indicated by their response or by the nature of their condition.

The most common serious complication in electric shock therapy is compression fracture of the thoracic portion of the spine. As has been mentioned, roentgenograms of the thoracic portion of the spine are taken before therapy to rule out the presence of pathologic changes in the bones which might predispose the patient to this complication. We have used curare routinely for our patients receiving electric shock, and we feel that chances for fracture are greatly reduced. It is rather impracticable to make a roentgenogram after each treatment. However, if the patient complains of any pain referable to the thoracic portion of the spine after a treatment, a roentgenogram is made before another treatment is given. It is of interest to note that Smith, Hughes, and Hastings,<sup>4</sup> who reported a series of 80 cases, had found four compression fractures which were asymptomatic and discovered on routine roentgen examination at the completion of the course of treatment. Another complication is dislocation, particularly of the shoulders and of the lower jaw. Defect of memory after treatment is fairly common, but it is a change into which the patient has insight. It is not a serious complication, and in our experience it always disappears. Muscular soreness may occur after the more severe convulsions. Headache is not uncommon, but it is rarely serious and it can be controlled with average doses of the ordinary analgesics. Nausea occasionally occurs, but vomiting is rare.

Restraint and postural measures are of value in preventing "jack-knifing," which supposedly causes compression fractures. It seems probable that "jack-knifing" is not the whole answer to compression fracture. The development of the skeletal musculature must play a large part in producing these compression fractures. Hence, postural precautions alone cannot be depended on to prevent this complication. Curare, which was first used by Bennett<sup>9</sup> in metrazol therapy,

<sup>5</sup> Jones, G. L., and Pleasants, E. N. Curare Modification of Therapeutic Convulsions, *Dis. Nerv. Syst.* **4** 17 (Jan) 1943.

<sup>6</sup> Evans, V. Metrazol Shock Therapy in Presence of Generalized Osteoporosis. Report of a Case, *Arch. Neurol. & Psychiat.* **46** 535 (Sept) 1941.

<sup>7</sup> Evans, V. Convulsive Shock Therapy in Elderly Patients: Risks and Results, *Am. J. Psychiat.* **99** 531 (Jan) 1943.

<sup>8</sup> Kay, F. A., Smith, J. D., and Reim, N. H. Electroshock Treatment in Psychiatric Disorders, *J. M. A. Alabama* **12** 129 (Nov) 1942.

<sup>9</sup> Bennett, A. E. Curare: A Preventive of Traumatic Complications in Convulsive Shock Therapy, *Am. J. Psychiat.* **97** 1040 (March) 1941.

comes near to eliminating compression fractures completely. Curare acts on the myoneural junction, probably by neutralizing acetylcholine, and thus prevents the response of striated muscle to the nerve impulse. For some reason, the intercostal muscles and the diaphragm are more resistant to the drug than the ordinary skeletal muscles. Therefore, one can calculate a dose that will soften the convulsion but will not interfere with respiration.

Most therapists have used curare only for those of their patients who seemed most susceptible to fracture. We have used it routinely and in smaller doses than those used by Bennett for metrazol therapy. Also, rather than use weight alone as an index for the dosage of curare, we have taken into consideration the general muscular development of the patient. We have found that 2 cc of curare given intravenously is the "working dose." This is the dose that will give satisfactory curarization of an adult weighing 140 pounds (63.5 Kg) and of average musculature. We have given between 1.5 and 3.5 cc. One minute is taken to inject the drug, and the treatment is given two minutes after the injection is completed.

The first 100 cases in which we have used the electric shock treatment cover a period of eleven months, hence the duration of the follow-up study varies between one and ten months. For the purpose of simplifying our statistics we have indexed the diseases of our patients as (1) depressions, (2) schizophrenia, (3) manic-depressive psychoses and (4) psychoneuroses. Obviously, there may be some overlapping. Included in the depressions are involutional melancholia, reactive depressions and depressions with mixed components, including menopausal symptoms. We have been interested especially in the immediate results obtained with electric shock. Even the most pessimistic observer must agree that it alters the psyche within a short time and makes possible a psychotherapeutic approach that may not have been possible before the treatment. The results in treatment of the reactive depressions, involutional melancholias and endogenous depressions, as classified by Fetterman,<sup>10</sup> are often dramatic. Two cases in point are briefly described.

**CASE 1**—C. B., a married man of 50, was admitted to the hospital on Dec. 31, 1942, with a history of having been extremely nervous for three months. In the three weeks preceding his admission he had become depressed and had mentioned suicide on several occasions. He had made vague statements of having embezzled funds from the city, for which he had worked some years in a responsible position.

A more detailed history, obtained from members of the patient's family, disclosed that the patient had held a nonpolitical job with the city for over twenty years. More recently the job had come under political influence, and apparently there had been some pressure to replace him. It finally became necessary for the patient to undergo competitive examinations to continue in his position. He passed these examinations with higher grades than his competitors, but he felt unable to accept his former responsibilities and resigned.

On admission to the hospital he was confused, agitated and suicidal. He was deeply depressed. Physical examination revealed nothing unusual except for evidence of vitamin C deficiency. He was treated symptomatically for twenty-five days and showed little improvement. On January 26 he was given his first electric shock treatment, and a grand mal reaction was obtained. He showed considerable improvement after this first treatment, and he was given two additional treatments, on January 28 and 29. After these he appeared completely changed. He took interest in his surroundings and began associating with fellow patients. His family stated that he was "his old self." He was discharged from the hospital on February 3. He has been followed in the outpatient clinic and has continued well. It was arranged that he return to work in a new position on June 1, 1943.

**CASE 2**—M. M., a married woman of 45, was admitted to the hospital as a psychiatric patient on Dec. 2, 1942. She was transferred to our care from one of the state hospitals for the insane, where she had been a patient for twelve months. Born in Scotland, she had come to the United States at 25 years of age and had married a short time later. At 31 years she gave birth to a son. Her marital life had been normal, and apparently she had always been a stable person until two months prior to her commitment to the state hospital. At that time she began quarreling over trivial matters with some of her relatives by marriage. After an argument with her sister-in-law she told her husband that she herself had been wrong and that God would punish her. She began to have many persecutory ideas and became highly agitated. She ate little and lost considerable weight. An attending physician advised hospitalization. Because of limited funds she was committed to the state hospital. During her twelve months in the state hospital she showed a change in her menstrual cycle and was treated symptomatically. She did not respond to such treatment. She continued to have persecutory ideas. Because the financial status of the husband had improved with the advent of defense work, he asked that his wife be transferred to our hospital for further treatment so that she could be nearer home.

Twelve days after her admission, on Dec. 14, 1942, the patient was given her first electric shock. After her third treatment she became rational, asked about her illness and seemed normal. She wrote her sister in Scotland the first letter she had written in over a year. Two days later she had a relapse and the shock treatment was continued. In all she was given eleven treatments, eight of which produced grand mal reactions and three of which produced equivalent reactions. Her improvement was dramatic, and, although further hospitalization was advised, the husband asked that his wife be given a trial at home. We consented to his request. On February 3 she was discharged from the hospital to the outpatient service. She had gained 13 pounds (5.9 Kg). She has continued to do well at home and has accepted the responsibility of her home.

<sup>10</sup> Fetterman, J. L. Electro-Coma Therapy of Psychoses, *Ann Int Med* 17:775 (Nov) 1942.

Of the 100 patients treated, 32 have had schizophrenia, 31, depressions, 25, psychoneuroses, and 12, manic-depressive psychoses

In recording our results we have placed the patients in three categories which we shall refer to as improved, less improved and least improved. In the improved group we have placed the patients who have improved to the extent that they are able to return to their former responsibilities. In the less improved group we have placed the patients who have improved but not to the extent that they are able to accept all of their former responsibilities. In the least improved category we have placed the patients who do not fit into either of the first two groups. Many of those placed in the least improved category had actually improved as compared with their condition on admission, but, nevertheless, they were unable to accept any responsibilities and had to be under further care either in an institution or at home.

The table graphically records our results

*Results of Treatment*

Illness Treated	Number of Patients	Im proved	Less Im proved	Total	Least Im proved
Schizophrenia	32	9 (28.1%)	15	24 (75%)	8
Depression	31	24 (77.4%)	3	27 (87%)	4
Psychoneurosis	25	6 (24%)	16	22 (88%)	3
Manic depressive psychoses	12	5 (41.7%)	2	7 (58.4%)	5

It is of interest to note that in the improved group there are only 9 of the 32 persons with schizophrenia treated, or 28.1 per cent. However, if the improved and the less improved group are combined, there are 24 of 32 treated, or 75 per cent. Of the patients with depression, there are 24 of 31 in the improved group, or 77.4 per cent. The percentage increases to 87 when the improved and the less improved group are combined. Of the 25 patients with psychoneuroses treated, only 6, or 24 per cent, can be placed in the improved group, while this figure rockets to 88 per cent for the combined group. Of the 12 patients with manic-depressive psychoses treated, 5, or 41.7 per cent, are in the improved group and 58.2 per cent in the combined category.

There is some question as to the usefulness of electric shock in treatment of the manic-depressive psychoses, and with only 12 patients in our series our data are insufficient for any conclusion. Reed<sup>11</sup> expressed the opinion that the therapy is of value in that it reduces the period of illness to a few weeks and encourages the patient to re-

turn immediately for treatment when the next attack occurs. Myerson<sup>12</sup> made the point that it does not seem advisable to give electric shock in cases in which the manic-depressive cycle repeats itself every few months or more often. Our impression is that electric shock is a valuable aid in the management of the highly manic or noticeably agitated depressed phase of this psychosis, but the treatment does not have the specificity that it has for the reactive depressions.

It is generally conceded that electric shock therapy is of doubtful value in the treatment of schizophrenia. This deduction receives support from our results when it is noted that only 28.1 per cent of the treated patients with schizophrenia can be placed in the improved group. However, the 75 per cent in the combined group suggests that the schizophrenic patient may be aided somewhat, often to the extent that he can be managed more easily by his family and can even accept some light responsibility.

Electric shock treatment of psychoneurotic patients has been discouraging in our experience. Our percentage in the improved category is low. It seems that psychotherapy is of greatest value in the treatment of the psychoneuroses and the only value of electric shock is to facilitate a better approach in a psychotherapeutic way.

Electric shock is an almost specific therapy for the depressions, as is reflected in the high percentage of (77.4 per cent) patients in the improved category and in the combined group (87 per cent).

In the comparatively short follow-up period relapses in our patients have not been frequent. Some with depressions who had a relapse responded well to a second and shorter course of treatment. Some of these relapses have been mild enough for the patients to continue with the treatment in the outpatient department.

Our complications in electric shock with the routine use of curare have been almost negligible. We have had 2 compression fractures of the thoracic portion of the spine. One of the fractures occurred in a large and muscular man who apparently was not sufficiently curarized by the prescribed dose. The other fracture was also in a male who had three treatments accompanied by the use of curare. As he was being prepared for his fourth treatment, he objected to the intravenous injection of curare, and, rather than force him to take the injection, we administered the treatment without the curare. Shortly after awakening from the treatment the patient began

11 Reed, G. E. The Electric Shock Therapy of Psychoses, *Canad. M. A. J.* 47:311 (Oct.) 1942.

12 Myerson, A. Further Experience with Electric-Shock Therapy in Mental Disease, *New England J. Med.* 227:403 (Sept. 10) 1942.

to complain of tenderness and soreness in the upper thoracic portion of his spine. A roentgenogram was taken, which showed a compression fracture of the fifth thoracic vertebra. Neither of these 2 patients had any untoward complications, and neither was placed in a body cast.

There were no dislocations or other fractures in our series, nor were there any other serious complications. For 1 patient we discontinued treatment because in both treatments given there occurred a cardiac arrest.

#### SUMMARY AND CONCLUSIONS

General hospitals with neuropsychiatric facilities can utilize electric shock therapy to advantage. In a general hospital of six hundred beds 100 patients were successfully treated over a period of eleven months.

Electric shock therapy has largely replaced metrazol convulsive therapy. It appears to be almost a specific therapy in the treatment of the

depressions whether they are endogenous, involuntal or reactive or depressions with mixed components. The therapy is not of great value for schizophrenia, although it does seem to make many of the patients more manageable. Its use for the manic-depressive psychoses is primarily to facilitate management. The use of this therapy for frequent recurrences of this psychosis is questionable. For the psychoneuroses the results are rather discouraging, probably because the underlying determinant must be removed to relieve the psychoneurotic state properly, electric shock is judged to be of some benefit in facilitating the psychotherapeutic approach.

Curare was used routinely in the treatment of our 100 patients. The only serious complication was compression fracture of the thoracic portion of the spine. This occurred in only 2 cases, and in 1 of these the fracture occurred when the curare was unwittingly omitted after it had been used in earlier administrations.



# USE OF A SYNTHETIC DIET FOR FOOD ALLERGY AND TYPHOID

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An attempt has been made to construct a diet for man as nearly as possible free of natural foods and composed of nutritional factors in chemically pure form. The need for such a diet may occur in three conditions. First, since a mixture of amino acids is not antigenic, one may support normal nutrition for persons with severe food allergy and at the same time determine whether food plays an important role in the manifestations of allergy exhibited by the patient. When the patient is allergic to food, the feeding of such a diet should result in definite improvement. Secondly, mixtures of amino acids and dextrose, since they are both crystalline, are rapidly absorbed in the upper portion of the intestinal tract. Pure fats may be emulsified so that they can be absorbed as rapidly as natural ones. Thus, when there is ulceration of the lower part of the intestinal tract one might expect such a diet to be more rapidly and easily absorbed than natural foods composed of proteins and starches. Thirdly, as when purified diets are fed to animals it may be possible to determine accurately the requirement for a single vitamin, both under normal circumstances and in pathologic conditions in which it is suspected that requirements are increased. The purpose of this paper is to record our experience in the use of a synthetic diet under two of these conditions: first, when given to patients with various types of allergy in whose cases there was some question whether food was an important factor and, secondly, to patients who were suffering from typhoid.

## NUTRIENTS AVAILABLE FOR MAKING A SYNTHETIC DIET

In 1935 Rose<sup>1</sup> discovered the last of the amino acids, threonine. This amino acid added to those already known made it possible to place rats on a nonprotein diet on which they could grow normally and reproduce. In 1940 Mueller,

Kemmerer, Cox and Barnes<sup>2</sup> produced an enzymatic digest of casein which would support the growth of experimental animals. This digest contains 12.5 per cent of nitrogen, of which 7.4 per cent is amino acids, the remainder presumably being composed of polypeptides. Guinea pigs could not be sensitized to the amino acid mixtures. Other workers<sup>3</sup> have shown that infants can be kept in nitrogen balance during both oral and parenteral administration of amino acid mixtures. McGee and Emery<sup>4</sup> studied the rate of absorption of the amino acid mixture from the small intestine of man by means of the Miller-Abbott tube. They showed that the amino acid mixture is absorbed twice as fast as casein or gelatin. Elman and his associates<sup>5</sup> have used the amino acid mixtures intravenously and have been able to support the metabolism of various patients who could not take food by mouth. They were able to keep patients in nitrogen equilibrium, and they have been able to give as much as 300 Gm intravenously in twenty-four hours without serious reactions.

Dextrose is obviously the best source for carbohydrate in such a food mixture. Its rate of absorption was studied by Cori<sup>6</sup> in animals

2 Mueller, A. J., Kemmerer, K. S., Cox, W. M., and Barnes, S. T. The Effect of Casein and a Casein Digest on Growth and Serum Protein Regeneration, *J Biol Chem* **134** 573, 1940.

3 Shohl, A. T., Butler, A. M., Blackfan, K. D., and MacLochlan, E. Nitrogen Metabolism During Oral and Parenteral Administration of the Amino Acids of Hydrolyzed Casein, *J Pediatr* **15** 469, 1939.

4 McGee, L. C., and Emery, E. S. Rate of Absorption of Amino Acids from the Small Intestine in Man, *Proc Soc Exper Biol & Med* **45** 475, 1940. Zetzel, L., Banks, B. M., and Sagall, E. Intestinal Absorption of an Amino-Acid Mixture in Patients with Chronic Idiopathic Ulcerative Colitis and Enterocolitis, *Am J Digest Dis* **9** 350, 1942.

5 Elman, R., and Weiner, D. O. Intravenous Alimentation with Special Reference to Protein (Amino Acid) Metabolism, *J A M A* **112** 796 (March 4) 1939. Elman, R. Protein Deficiency in Surgical Patients and Its Correction, *J Am Dietet. A* **18** 141, 1942. Parenteral Replacement of Protein with the Amino Acids of Hydrolyzed Casein, *Ann Surg* **112** 594, 1940.

From the Department of Internal Medicine, Washington University School of Medicine.

1 Rose, W. C. The Nutritive Significance of the Amino Acids, *Physiol Rev* **18** 109, 1938.

(Footnotes continued on next page)

and later by Groen<sup>6</sup> in man by means of the Miller-Abbott tube. The latter observer confirmed Cori's results for animals, showing that dextrose is rapidly absorbed from the first part of the small intestine. It is absorbed at such a rapid rate that the question of flooding the blood with it has to be considered. To avoid too rapid absorption the feeding tube is admirably suited, since smaller feedings can be given hourly or at two hour intervals continually throughout the twenty-four hours.

The fat in a mixture of purified food materials presents a more difficult problem than that of the nitrogen or the carbohydrate. Glycerides of pure fatty acids have not been available to us, but the oils of corn, olive and hydrogenated cottonseed are available and not expensive. Tottingham<sup>7</sup> has given the analysis of these oils and stated that in corn oil and cottonseed oil there are about 40 per cent of linoleic acid and small amounts of arachidonic acid. Since it has been shown that linoleic and arachidonic acids are acids which animals cannot synthesize, one has in these oils an abundant source of the essential fatty acids. There is no way of accelerating the absorption of fatty acids from the intestinal tract, because bile and lipase are necessary for that operation, but emulsification is the initial step in the process of absorption, and it can be easily accomplished when one is making up the feeding mixture.

In using a mixture of amino acids, dextrose and corn or cottonseed oil as a source for the purified nutrients, one must add the inorganic nutrients in the form of a salt mixture. The amino acids cystine and methionine contain sulfur, and in the amounts of the amino acid mixture that we use there would be about 600 mg available in twenty-four hours. Requirements for the human adult are probably in the region of from 600 to 1,000 mg.<sup>8</sup> The other inorganic elements that are essential to human nutrition are calcium, phosphorus, magnesium, sodium, potassium, chlorine, iron, copper, zinc, manganese, iodine, fluorine and cobalt. In the ordinary diet all these inorganic elements occur in sufficient amounts in natural foods, except, of course, sodium and chlorine. Most of the re-

quirements of these elements are fairly well known, so that a salt mixture for human requirements can be put together without much difficulty. We have tried Cowgill's<sup>9</sup> salt mixture which he has fed to dogs but have found that it exerts a cathartic action when given to man. Table 1 gives the mixture of salts we have used,

TABLE 1—Salt Mixture (Twenty-Four Hour Requirement)

	Gm		Gm
Calcium phosphate	1.75	Potassium chloride	1.50
Calcium carbonate	0.80	Sodium acid phosphate	2.50
Potassium acid phosphate	2.50	Sodium chloride	5.50
Potassium acid carbonate	4.00	Manganese carbonate	1.00
Trace Elements			
	Mg		Mg
Ferrous sulfate	100	Copper sulfate	2.5
Potassium iodide	0.065	Zinc sulfate	2.5
Manganous sulfate	0.30		

and table 2 shows the daily supply of elements that this mixture supplies. The mixture has been used for a number of persons, both normal and sick, and found to be noncathartic.

The following vitamins are available in purified form: carotene (provitamin A), activated ergosterol, menadione (2-methyl-1,4-naphthoquinone), thiamine, riboflavin, nicotinamide, pyridoxine, calcium pantothenate, ascorbic acid and choline chloride. Some of these ten vitamins are known to be required by the human being, while others may be needed under stress of a severe infection. It has been shown that biotin is needed only when excessive amounts of egg

TABLE 2—Elements Supplied by 19.655 Gm. of Salt Mixture (Twenty-Four Hour Requirement)

	Gm		Mg
Calcium	1.00	Iron	20
Phosphorus	1.48	Iodine	0.05
Potassium	3.06	Manganese	0.10
Sodium	2.58	Copper	1.0
Chlorine	4.00	Zinc	1.0
Magnesium	0.29		

white have been fed to human beings,<sup>10</sup> just as it is required by experimental animals. Inositol is an alcohol widely present in muscle and many tissues and has been shown to be a vitamin essential for the mouse.<sup>11</sup> Whether the

6 Cori, C. F. The Rate of Adsorption of Hexoses and Pentoses from the Intestinal Tract, *J. Biol. Chem.* **66** 691, 1925. Groen, J. The Adsorption of Hexoses from the Upper Part of the Small Intestine in Man, *J. Exper. Med.* **16** 245, 1936. Absorption of Glucose from Small Intestine in Deficiency Disease, *New England J. Med.* **218** 247, 1938.

7 Tottingham, W. E. *Plant Biochemistry*, Minneapolis, Burgess Publishing Company, 1937, pp. 66.

8 Sherman, H. C. *Chemistry of Food and Nutrition*, ed. 6, New York, The Macmillan Company, 1941.

9 Cowgill, G. R. An Improved Procedure, for Metabolism Experiments, *J. Biol. Chem.* **56** 725, 1923.

10 Sydenstricker, V. P., Singal, S. A., Briggs, A. P., De Vaughn, N. M., and Isbell, H. "Egg White Injury" in Man and Its Cure with a Biotin Concentrate, *J. A. M. A.* **118** 1199 (April 4) 1942.

11 Woolley, D. W. A New Dietary Essential for the Mouse, *J. Biol. Chem.* **136** 113, 1940.

human being can synthesize it is not known. Vitamin E has not been shown to be essential for the human being<sup>12</sup>. Probably the most essential of the vitamins have been discovered, but undoubtedly there are others which man may need to a lesser degree than those that are now known. One can safely give a synthetic diet to which these ten vitamins have been added for a period of two weeks, especially at a time when the metabolism of the patient is normal. However, if there is infection or elevation of metabolism it is probably necessary to add a liver concentrate, so that other vitamins now unknown will be present in the food mixture. The liver

TABLE 3—Caloric Value of Synthetic Diet

Calories	24 Hr Volume, Cc	Amino Acids,* Gm	Fat, Gm	Dextrose, Gm	Salt Mixture, Gm
1,500	1,080	42	84	150	16
2,000	1,440	56	112	200	16
2,500	1,800	70	140	250	20
3,000	2,160	84	168	300	24
3,500	2,620	98	196	350	28
4,000	2,880	112	222	400	32

\* Amigen, furnished by Mead Johnson & Co., Evansville, Ind.

extract that we have employed has been widely used in this manner for animals. Choline is added to the diet because it has been shown in experimental animals that larger amounts of choline than can be synthesized<sup>13</sup> are needed by the fast-growing animal, and, since the metabolism in fever is greatly elevated, it is well that there should be a ready supply of the methyl groups from choline.

#### PREPARATION OF THE DIET

A master diet of 2,500 calories containing 70 Gm of amino acids, 140 Gm of oil, 250 Gm of dextrose and 20 Gm of the salt mixture is made up to a volume of 1,800 cc. By feeding less or more of this standard mixture the calories can be varied from 1,500 to 4,000, as table 3 shows. This standard technic makes the work of the dietitian simple, however, a mixture of amino acids, fat and dextrose may be made up in almost any volume desired.

The dextrose, amino acids and salt mixture are dissolved in 1,000 cc of tap water by the use of a mechanical mixture. Eight grams of powdered pure

gelatin is dissolved in 75 cc of warm tap water and allowed to stand twenty minutes so that the gelatin will be completely dissolved, then the gelatin solution is beaten in a mechanical mixer or with a Dover beater and the oil is added, in the beginning in small quantities. When all the oil is emulsified, it is diluted with the solution of dextrose, amino acids and salts and the total volume made up to the desired quantity with water. We have found that corn oil and cottonseed oil are emulsified easily and remain in emulsion well, this is not so true of olive oil. Undoubtedly the salts aid materially in the emulsification and the stability of the emulsion. Since gelatin is a substance to which few persons are allergic, it is our material of choice as an emulsifier. Agar is better in many respects, but we have found it too cathartic. The other hemicelluloses that have been tried have not been satisfactory.

The vitamins are given by the nurse in charge of the patient. Table 4 shows the doses of vitamin and vitamin materials used under the two conditions we are discussing. Thiamine, riboflavin, nicotinamide, pyridoxine and calcium pantothenate were given in the form of a tablet. This tablet contained 5 mg of thiamine and riboflavin, 25 mg of nicotinamide and calcium pantothenate and 10 mg of pyridoxine. For convenience it is referred to as TRN 6 P. It will be noted that the daily dose of the five crystalline members of the B

TABLE 4—Dosage of Vitamins

For Normal or Allergic Persons	
Vitamin A (carotene)	10,000 U S P units
Vitamin D (activated ergosterol)	500 U S P units
*Thiamine	5 mg
Riboflavin	5 mg
Nicotinamide	25 mg
Pyridoxine	10 mg
Calcium pantothenate	25 mg
For Patients with Typhoid	
Vitamin A (halibut liver oil)	60,000 U S P units
Vitamin A (halibut liver oil)	5,000 U S P units
*Thiamine hydrochloride	10 mg
Riboflavin	10 mg
Nicotinamide	50 mg
Pyridoxine	20 mg
Calcium pantothenate	50 mg
Ascorbic acid	200 mg
Choline chloride	1 Gm
2 methyl 1,4 naphthoquinone (menadione)	2 mg
†Liver powder	20 Gm

\* Thiamine hydrochloride, riboflavin, nicotinamide, pyridoxine and calcium pantothenate furnished by Merck & Co., Inc., Rahway, N. J.

† Liver powder furnished by Wilson & Co., Inc., Chicago. Dr. David Klein informed us that this powder contains per gram 10 U S P units of vitamin B<sub>12</sub>, 325 micrograms of riboflavin, 500 micrograms of pantothenic acid, 40 micrograms pyridoxine and 15 milligrams of nicotinic acid. In addition, it contains choline and a large number of other factors not as yet precisely defined.

complex is large. We believe these amounts desirable because in many instances food allergy results in voluntary restriction of the vitamin-rich foods. Table 5 gives the schedule of vitamin supplements as administered both to patients with typhoid and to allergic persons.

The taste of this mixture is not pleasant. Though some persons were found who did not mind taking it by mouth, most persons find it offensive. For this reason a no. 12 Levin tube was inserted into the stomach and left in place during the course of the feedings. Feedings were given at intervals of two to four hours.

12 Mattill, H. A. Vitamin E, J. A. M. A. 110:1831 (May 28) 1938. Fleischmann, W. Creatine-Creatinine Excretion in Neuromuscular Diseases Treated with Alpha-Tocopherol and with Testosterone, Proc. Soc. Exper. Biol. & Med. 46:94, 1941.

13 McHenry, E. W. Choline, the B Vitamins and Fat Metabolism, Biol. Symposia 5:177, 1941. Griffith, W. H. The Relation of Choline to the Kidneys, ibid. 5:193, 1941. Glick, D. The Nature and Significance of Cholinesterase, ibid. 5:213, 1941. du Vigneaud, V. Interrelationships Between Choline and Other Methylated Compounds, ibid. 5:234, 1941.

## USE OF SYNTHETIC FEEDING IN ALLERGY

As a cause for the manifestations of allergy, food is often an important factor, especially when these manifestations involve the skin or the intestinal tract<sup>14</sup> The diets suggested by Rowe<sup>15</sup> for the elimination of most of the troublesome

TABLE 5—*Schedule of Vitamin Supplements for Patients with Typhoid*

Time of Feeding	Vitamins to Be Added	
7 a m	1	5 drops halibut liver oil
	2	1 mg 2 methyl 1,4 naphthoquinone (menadiolone)
	3	1 teaspoon choline chloride solution (1 Gm)
	4	1 tablet T R N 6 P crushed
9 a m	1	5 drops halibut liver oil
	2	1 ascorbic acid tablet crushed
11 a m	1	5 drops halibut liver oil
	2	1 ascorbic acid tablet crushed
1 p m	1	5 drops halibut liver oil
	2	1 teaspoon choline chloride solution (1 Gm)
	3	20 Gm of liver powder
3 p m	1	5 drops halibut liver oil
	2	1 ascorbic acid tablet crushed
5 p m	1	5 drops halibut liver oil
	2	1 ascorbic acid tablet crushed
7 p m	1	5 drops halibut liver oil
	2	1 mg 2-methyl 1,4-naphthoquinone
	3	1 teaspoon of choline chloride solution (1 Gm)
	4	1 tablet T R N 6 P crushed
9 p m	To each of these feedings 5 drops of halibut liver oil is added	
11 p m		
1 a m		
3 a m		
5 a m		

foods are without doubt useful, but if any criticism can be made it is that they are not usually adequate in calories, calcium or vitamins A and C, and care is necessary to prevent malnutrition. Also, the physician never knows whether the patient may not be one of the rare persons who are sensitive to one or more of the foods which make up the Rowe diets. When the physician wishes a diet to fulfil two requisites, namely, one that is adequate in calories, minerals and the important vitamins and at the same time furnishes nitrogen free from protein (except for a small amount of gelatin), a synthetic diet such as suggested will be found most useful. The following brief case histories illustrate the types of patients to whom the diet has been given, and table 6 summarizes the data.

CASE 1—A 15 year old girl entered the hospital because of a dermatitis of fourteen years' duration. The dermatitis covered the wrists, backs of the hands, popliteal spaces and ankles. The skin was rough, with reddened areas and many scratch marks, and was covered with hemorrhagic crusts. About two years previously the patient had had two attacks of asthma. There was also a history of vomiting after eating spinach or eggs. The dermatitis was improved in the summer or when she was exposed to ultraviolet radiation.

14 Hampton, S F. Henoch's Purpura Based on Food Allergy, *J Allergy* **12** 579, 1941.

15 Rowe, A H. Elimination Diets and the Patient's Allergies, Philadelphia, Lea & Febiger, 1941.

Tube feedings were continued for twenty-three days, and no improvement was noticeable. Later treatment with human dander extract and hemolytic *Staphylococcus aureus* vaccine produced definite improvement.

CASE 2—A woman of 38 entered the hospital because of eczema of the face, neck, ears and axillas and to a less extent the whole body. Her skin was thickened, dry and reddened and in places covered with bloody crusts. Tube feedings were carried out for five days, immediate improvement was striking.

CASE 3—A woman of 51 entered the hospital because of purpura. A fine purpuric rash was distributed over the whole body. She was able to take the feedings by mouth, and they were continued for eleven days. The purpura faded rapidly and had entirely disappeared by the end of a few days. There was a reappearance of the purpura following the use of carmine capsules, but again the purpura disappeared rapidly. The final decision was that the purpura was probably of food origin, the relapse being due to the dye.

CASE 4—A woman aged 20 entered the hospital with bronchial asthma. The asthma was thought to be intrinsic. It had been present since the age of 8 years. There was a definite bacterial infection of the sinuses. The diet was given for five days, and there was some improvement during that time. She was able to do without epinephrine, although its use had been constant.

This case illustrates the fact that even in bronchial asthma, food may be of minor but of some importance from a therapeutic viewpoint.

TABLE 6—*Data for Allergic Patients Given Synthetic Diet*

Diagnosis, Sex and Age (Yr)	No of Days Diet Taken	Method of Administration	Progress While on Diet	Foods as an Etiologic Factor
Neurodermatitis ♀ 15	23	Tube	No improvement	None
Eczema ♀ 38	5	Tube	Improvement rapid	Important
Purpura ♀ 51	11	Mouth	Improvement rapid	Important
Bronchial asthma ♀ 20	5	Mouth	Improvement	Minor but definite
Colitis (allergic) ♀ 43	2	Tube	Complete relief	Complete
Neurodermatitis ♀ 36	12	Tube	Improvement	Important
Henoch's purpura ♀ 15	14	Tube	Great improvement	Important
Colitis, purpura ♀ 35	3	Tube	Complete relief	Complete
Purpura (abdominal pain) ♀ 20	14	Tube	Partial relief	Minor or none

CASE 5—A woman of 48 came into the hospital because of spells of diarrhea which had been present for six to seven years, and at the time of admission the diarrhea had been constant. The barium sulfate enema showed the colon to be extremely irritable, with deep irregular haustra. Tube feedings were carried out for only two days, but as soon as the mixture was given the diarrhea stopped immediately. Observations following the tube feedings showed that the patient was allergic to corn, celery, peas, cabbage, milk, beans, bran and coconut.

CASE 6—A Negro woman of 36 entered the hospital because of neurodermatitis. The lesion involved the elbows and the popliteal spaces. A great deal of lichenification was present. The eosinophil count was 16 per cent. Tube feedings were continued for twelve days. The improvement was slow but steady, and it was thought that the case illustrated the type of neurodermatitis responding to the elimination of foods to which the patient was sensitive.

CASE 7—A child 15 years old entered the hospital because of Henoch's purpura. Tube feedings were given for fourteen days. The abdominal pain ceased abruptly, the purpura of the skin cleared, and the symptoms of colitis improved rapidly. It was found that the patient was sensitive to milk. She was discharged from the hospital, but after a period of complete freedom from symptoms she again ingested large amounts of milk. This was followed by a return of her symptoms, and when she entered the hospital for the second time she was extremely ill, showing severe ascites, a great reduction in the plasma albumin, an enlarged spleen and an intense bloody diarrhea. Again the patient was given tube feedings, and large amounts of vitamins were administered—15 mg daily of thiamine and riboflavin, 75 mg of nicotinamide, 30 mg of pyridoxine and 75 mg of pantothenic acid. In addition, the liver concentrate was given. Proctoscopic examination showed at the beginning pronounced edema with petechial hemorrhages of the mucosa but no ulceration. At the end of her treatment the mucous membrane was entirely normal, the proctoscope was introduced 20 cm and it was noted that the colon was extremely irritable to touch, the slightest injury causing some bleeding. The roentgen diagnosis was typical ulcerative colitis.

The case illustrates the secondary effects of long-continued allergic colitis. The roentgen picture, typical of ulcerative colitis, was apparently due to the edema of the walls of the colon.

CASE 8—A white woman of 35 entered the hospital because she was anxious and upset as to what she should eat. She had lost 20 pounds (9.1 Kg) in weight and showed purpuric hemorrhages over the skin. She complained bitterly of abdominal pain. The tube feedings were given for three days. Pain ceased immediately, both subjectively and to abdominal palpation. The purpura disappeared.

CASE 9—A girl 14 years of age entered the hospital with a history of abdominal pain, hemorrhagic diarrhea and purpura of the skin. These symptoms were alarmingly intensified during her menstrual period. At that time the abdomen was greatly distended, the pain had to be controlled with opiates, there was angioneurotic edema of the face and the diarrhea was greatly intensified. It was found that the purpura was associated with an ascorbic acid level of zero in the blood. Also, the purpura in subsequent menstrual periods failed to occur when the ascorbic acid level of the blood was raised. With tube feedings the abdominal pain improved but did not entirely disappear. Furthermore, the following menstrual period was extremely severe, and the symptoms of pain, abdominal distention, diarrhea and angioneurotic edema reappeared. The unsatisfactory improvement with tube feeding led to the conclusion that the patient had an intrinsic allergy and that she was undoubtedly sensitive to bacteria, her symptoms being intensified with infection. The intensification of the symptoms during menstruation was explained by the possibility of endometriosis in an unusually allergic person.

The case illustrates the value of tube feedings in ruling out sensitization to food in a difficult situation.

The change in the patient's manifestations of allergy when the diet has been administered a few days is of use in estimating the importance of food as an etiologic factor. In some cases the improvement is rapid and dramatic, while in other cases, especially of some types of eczema, progress is slow. However, after a week's use of a synthetic diet one can usually decide fairly accurately the role food is playing in the manifestations of allergy. When no improvement in the symptoms and the physical condition of the patient occurs, food as a factor can be dismissed and the patient returned to his usual diet. The ruling out of the food factor emphasizes the search for the causes in other fields. If improvement indicates that food is to some degree important, such essential foods as wheat, milk and eggs may be added one at a time to the mixture or given by mouth.

#### USE OF THE DIET FOR PATIENTS WITH TYPHOID

The regulation of the diet continues to be of prime importance to the welfare of the patient with typhoid. Since the work of Shaffer and Coleman<sup>16</sup> the importance of adequate nutrition in typhoid has been recognized, and the studies of Coleman<sup>16</sup> indicate that the clinical course of patients given high caloric diets is more favorable than that of patients subjected to partial starvation. At the present time an extensive clinical and experimental literature has accumulated on the general subject of the effect of nutritional deficiency on resistance to infection,<sup>17</sup> and most of the evidence indicates that the body is more susceptible to infection when the diet is inadequate. Moreover, the evidence suggests that the requirements for calories, protein, thiamine, riboflavin, nicotinic acid and ascorbic acid are increased during infections.

It is generally agreed that a diet for patients with typhoid should be low in residue<sup>18</sup> so as to

16 Shaffer, P. A. Metabolism in Typhoid Fever, *J. A. M. A.* 51:974 (Sept 19) 1908. Shaffer, P. A., and Coleman, W. Protein Metabolism in Typhoid Fever, *Arch. Int. Med.* 4:538 (Dec) 1909. Coleman, W. The Influence of the High Calory Diet on the Course of Typhoid Fever, *J. A. M. A.* 69:329 (Aug 4) 1917.

17 Robertson, E. C. The Vitamins and Resistance to Infection, *Medicine* 13:123, 1934. Perla, D., and Marmorston, J. Natural Resistance and Clinical Medicine, Boston, Little, Brown & Company, 1941, sect. 7.

18 Paullin, J. E., and Minnich, W. R., in Barr, D. P. Modern Medical Therapy in General Practice, Baltimore, Williams & Wilkins Company, 1940, pp. 1212-1220.

minimize work and trauma of an ulcerated intestine This synthetic diet has almost no residue

High caloric feeding in practice is found to be difficult, since patients with typhoid have no appetite and little if any desire for food A great deal of persuasion is needed, and the nurse or dietitian must spend much time, in fact, often hours, persuading the patient to ingest the required number of calories Since the synthetic diet was given by indwelling stomach tube, the amount of nursing service required for its administration was greatly reduced

It will be noted that the doses of vitamins given to patients with typhoid were massive and probably in excess of their actual requirements, but the decision to err on the side of too much rather than too little was based on the following

Eleven patients were given the diet during the summer of 1941, and some of the clinical observations made are summarized in tables 7 and 8 In all but 2 cases, diagnosis was established by positive cultures of stool, blood or both Five patients gained weight during the time of tube feeding (1 e, febrile period usually) Four patients lost weight (greatest loss of weight, 5½ pounds [2.5 Kg]) Two were too sick to be weighed Loss of weight occurred in patients who were obese to begin with Other forms of treatment consisted of use of sulfonamide compounds, transfusions and convalescent serum Seven patients had nervous manifestations, such as headache, tremor and stupor These gradually disappeared as the disease subsided An important observation was that there was no abdominal

TABLE 7—Data for Patients with Typhoid

Patient	Age, Yr	Sex	Height In	Calculated Basal Calories	Days of Tube Feeding	Calories per Day by Tube	Amount per Feeding, Cc	Weight Before Feeding, Lb	Weight After Feeding, Lb
W K	19	M	68	1,520	7	3,000	180	107	106
J N	11	M	55	1,300	20	2,500	150	61	62½
R G	10	M	55	1,260	7	2,500	150	57½	56
A B	23	M	68	1,900	7	3,500	210	200	198¾
E D	30	F	63	1,300	22	3,000 (12)* 3,500 (9)	180 (12) 210 (9)	114½	120¼
G C	40	F	63	1,250	23	3,000	180	114	123
f					27	3,000	180		121
F C	6	M	47	1,075	25	2,083 (12) 2,500 (13) 3,000 (14)	125 (12) 150 (13) 210 (14)	37	41¾
N A	35	M	71	1,725	19	3,000 (5) 3,500 (14)	180 (5) 210 (14)	145	147
J J	33	M	72	1,900	16	3,000	180	195	189½
P E	16	F	66	1,660	18	3,000 (16)	180	†	147½
f					15	3,000	180		143
I B	61	F			28	3,000	180	‡	

\* Number of days in parentheses  
† Fed again during a relapse  
‡ Too sick to be weighed

considerations 1 There is indication that the requirements of vitamins are increased in such a toxic febrile state, and the extent of this increase is not known 2 By the time the diagnosis is made, the patient may have gone for a number of days without adequate food owing to poor appetite and a nutritional deficit may have developed 3 There may be some question of complete absorption, especially if there is diarrhea<sup>19</sup> 4 It has been suggested that some of the clinical manifestations of the disease may be due at least partially to vitamin deficiency and not to the toxic aspects of the infection itself 5 No harm can result from giving amounts greater than the actual requirements

distention One patient had slight transient tympany, and 1 had severe distention on entry which subsided promptly during the first week There were relapses in 2 patients Although there was variation in the duration of the fever, this could not be seen to have been changed by the diet

Vomiting of one or two feedings per twenty-four hours sometimes occurred during the course of the highest febrile period but was rare after defervescence had begun Patients usually had one or two, occasionally more, fluid greenish stools per day during the febrile period The daily enema was usually not necessary Abdominal cramps were rare

A few patients complained of pain in the throat, substernally or in the abdomen following feedings These same patients could be fed at night during sleep without being awakened,

19 Bean, W B, and Spies, T D Vitamin Deficiencies in Diarrheal States, J A M A 115 1078 (Sept 28) 1940 Dann, M, and Cowgill, G R Influence of Diarrhea on the Vitamin B<sub>1</sub> Requirement, Arch Int Med 62 137 (July) 1938



hence no importance was attached to these symptoms

The experience with patients with typhoid shows that the synthetic diet can be given successfully and apparently satisfactorily. We were impressed by the fact that there was no significant loss of weight, that often there was a gain. This was found also by Coleman<sup>20</sup> with high caloric diets of natural foods. The absence or rapid disappearance of abdominal distention was also noteworthy. This was attributed to the rapid absorption of dextrose and amino acids

elimination of all but a minimum of residue. Because of this the diet appears to merit further trial.

#### COMMENT

We have not had an extensive experience with the use of this diet for ulcerative colitis, but experience with a patient who has been lately under observation has been impressive. The diet was given through a nasal tube for a period of four weeks. During this time he was extremely ill with high fever and had from sixteen to twenty stools a day. In spite of the great

TABLE 8—*Patients with Typhoid*

Patient	Diagnosis and Basis for It	Other Forms of Treatment	Nervous Manifestations	Distention	Complications
W K	Paratyphoid B, rising titer	None	None	None	None
J N	Typhoid, positive cultures of blood and stool	Transfusion of convalescent blood	Headache before diet, tremor at first	None	Occult blood in the stool
R G	Cultures of blood and stool yielded <i>Salmonella enteritidis</i> , typhoid and paratyphoid agglutinins	Sulfaguanidine before entry	None	None	None
A B	Typhoid, positive cultures of blood and stool	None	None	None	Pain in the right side of neck
E D	Typhoid, positive cultures of blood and stool	Intradermal typhoid vaccine when afebrile	None	Slight transient tympany	Three relapses, tube feeding during the last
G C	Typhoid, positive cultures of blood and stool	Transfusion sulfaguanidine before entry	Tremor of out stretched hands*	None	Relapse
F C	Typhoid, positive cultures of stool	Sulfadiazine	Delirium before entry, gradually became rational and cooperative	None	Malnutrition negativism and refusal of food on entry
N K	Typhoid, positive cultures of blood and stool	Convalescent serum	Apprehension, headache	None	Scrotal ulcer, occult blood in stool
J J	Typhoid, positive cultures of blood and stool	Sulfathiazole and quinine before entry	Headache	None	Trace of occult blood in stool
P E	Typhoid, positive cultures of stool	Transfusions, convalescent serum	Stupor which gradually disappeared		Massive intestinal hemorrhage before feedings were started relapse, anemia
I B	Typhoid, positive cultures of blood and stool	Sulfadiazine	Deep stupor	Severe on entry subsided gradually in one week	Dyspnea and rales at the lung bases glossitis

\* Headache and mild typhoid state before diet

high in the intestinal tract, leaving no carbohydrate for fermentation in the lower portion of the tract.

The results for typhoid were good, but they cannot be said to have demonstrated conclusively the superiority of this diet over others now in use in the treatment of this disease, since this would require controls and an extensive study carried over many years. However, the diet does carry out more than any other the two main principles recognized to be important in a diet for typhoid, namely administration of adequate amounts of the various nutritional factors and

loss of fluid and nutrients, his nutrition was well preserved. Experience of this sort leads us to believe that a synthetic diet of this nature will often prove life saving. We suggest that the fat be kept low and that, as other observers<sup>21</sup> have suggested with regard to protein, the amino acids be fed in amounts from 150 to 200 Gm a day and dextrose from 300 to 400 Gm. In this patient there was no distention. Undoubtedly

20 Coleman, W. Weight Curves in Typhoid Fever, *Am J M Sc* **144** 659, 1912

21 Mackie, T. T. The Medical Management of Chronic Ulcerative Colitis, *J A M A* **111** 2071 (Dec 3) 1938. Stickney, J. M., Heilman, F. R., Barger, J. A., and Dearing, W. H. Sulfaguanidine in Ulcerative Intestinal Diseases, *Proc Staff Meet, Mayo Clin* **17** 33, 1942.

more experience in the use of the diet for various forms of ulcerative colitis will be of interest

Since much of the fighting during the present war is occurring in tropical regions, the incidence of various types of infectious diarrhea with lesions of the lower part of the intestinal tract is likely to be high. There is a possibility that this diet may prove to be useful under such conditions, especially since its ingredients are desiccated and concentrated to the highest extent.

#### SUMMARY

A purified diet composed of amino acids, dextrose and emulsified oil to which is added a salt mixture and crystalline vitamins is suggested

as of use in three possible conditions: first, for patients with food allergy; second, for patients with severe infections of the intestinal tract; and, third, as a means of determining the requirements for certain of the vitamins.

Our experience with the use of this diet for patients with allergy leads us to believe that it is a useful tool among others to determine whether or not a patient is sensitive to food, at the same time fully maintaining his nutrition. The principles on which the use of the diet rests indicate its usefulness for typhoid and other ulcerative lesions of the lower part of the intestinal tract.

The staffs of Barnes Hospital and of the St. Louis City Isolation Hospital cooperated in these studies.

# Progress in Internal Medicine

## DISEASES OF THE LIVER AND BILIARY TRACT

### HEPATIC INVOLVEMENT IN VARIOUS DISEASES RELATED TO THE WAR

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The global extent of the present war has brought the various aspects of tropical diseases to the attention of members of the medical profession with renewed emphasis. Medical officers with troops are concerned primarily with the acute phases of such diseases. Civilian physicians, on the other hand, will be more interested in the chronic phases, found in soldiers after discharge from the army or brought back to the civilian population by the troops. Numerous articles, such as that of Faust,<sup>1</sup> have reviewed this field and called attention to the public health hazards concerned.<sup>2</sup> In the present review reference will be limited to the evidence of hepatic involvement by these various conditions.

#### MALARIA

Malaria constitutes the most widespread hazard and the most serious infectious disease for the military forces of the United States. Particularly in the northern and western sections of this country it now is relatively uncommon and most of the patients seen have mild forms. However, it is recognized that enlargement and tenderness of the liver may occur in the course of the disease. Jaundice is one of the cardinal signs in black water fever. Pathologists have long described extensive alteration in the histologic appearances of the liver in fatal cases. The past year Kopp and Solomon<sup>3</sup> have described alteration in the reactions to various functional tests (bromsulphalein, cholesterol, hippuric acid and cephalin flocculation) in cases of therapeutic malaria. These tests showed a return to normal function within three to six weeks.

Greene and Bruger<sup>4</sup> reported that the result of the cephalin flocculation test of Hanger was

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1 Faust, E. C. Disease in the Tropical War Zones, *Gastroenterology* **1** 995 (Nov.) 1943

2 Most, H., and Meleney, H. E. Falciparum Malaria. The Importance of Early Diagnosis and Adequate Treatment, *J. A. M. A.* **124** 71 (Jan. 8) 1944

3 Kopp, I., and Solomon, H. C. Liver Function in Therapeutic Malaria, *Am. J. M. Sc.* **205** 90 (Jan.) 1943

strongly positive in 2 cases of therapeutic malaria without jaundice. I have personally seen 1 other patient with dementia paralytica in whom benign tertian malaria was induced. Before the course of chills was completed marked icterus developed, with an enlarged and tender liver, and the patient died with the clinical picture of an acute hepatitis and hepatic insufficiency.

More recently Mirsky, von Biecht and Williams<sup>5</sup> have reported a series of 10 cases of malaria. The bromsulphalein test gave a positive result in only 20 per cent of the cases in which it was used. The cephalin flocculation test, on the other hand, gave a positive result in all. Because of this, Mirsky and his associates emphasized the importance of diet and measures to improve the status of the liver during both the acute and the convalescent period of the disease.

#### INFECTIOUS JAUNDICE

Jaundice has been known since antiquity in both sporadic and epidemic forms. The review of Ottenberg and Spiegel<sup>6</sup> reemphasizes the variety of infectious and chemical agents which may produce hepatic injury and so give rise to this symptom. Weil's disease, or leptospiral jaundice, was the first type of jaundice in which a specific infectious agent was recognized. Yellow fever has been recognized clinically for many years, but the identification of the specific causal virus has been recent.

That acute hepatitis, whether epidemic or sporadic, is a specific infectious disease was stressed by Cockayne<sup>7</sup> and later by Pickles.<sup>8</sup> American epidemics were reported by Hiscock

4 Greene, C. H., and Bruger, M. The Functional Study of the Liver and Its Clinical Evaluation, *New York State J. Med.* **43** 318 (Feb. 15) 1943

5 Mirsky, I. A., von Brecht, R., and Williams, L. D. Hepatic Dysfunction in Malaria, *Science* **99**: 20 (Jan. 7) 1944

6 Ottenberg, R., and Spiegel, R. The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents, *Medicine* **22** 27 (Feb.) 1943

7 Cockayne, E. A. Catarrhal Jaundice, Sporadic and Epidemic and Its Relation to Acute Yellow Atrophy of the Liver, *Quart. J. Med.* **6** 18, 1912

8 Pickles, W. N. Epidemic Catarrhal Jaundice Outbreak in Yorkshire, *Brit. M. J.* **1** 944 (May 24) 1930, Epidemic Catarrhal Jaundice, *Brit. J. Child Dis.* **33** 192 (July-Sept.) 1936

and Rogers<sup>9</sup> and by Blumer<sup>10</sup> More recent epidemics have been reported by Ottenberg and Spiegel<sup>6</sup> in the United States, Ford<sup>11</sup> and Evans<sup>12</sup> in England and Leffkowitz<sup>13</sup> in Palestine

Of particular interest is the account by Marchand<sup>14</sup> of health conditions in an isolated Indian village in the Yukon territory brought into contact with the outside world by the construction of the new Alaskan Military Highway The previously healthy village was forthwith swept by epidemics of measles, dysentery, whooping cough, mumps, meningococcic meningitis and catarrhal jaundice This is evidence both for the infectious nature of the jaundice and for the presence of healthy carriers among the urban workmen brought to the Indian village

Willcox<sup>15</sup> called attention to the military importance of infectious jaundice in troops during the last war, especially on the eastern front Military epidemics have been reported in the present war by Cameron<sup>16</sup> In the majority of these epidemics water, milk and foods apparently could be excluded as sources of infection Close contact with other persons suffering from the disease was the rule The incubation period varied from three to five weeks, with an average of twenty-eight to thirty-one days

The reports of different epidemics vary in details but agree that there is a prodromal period of three to ten days The prodromata frequently are associated with symptoms in the upper respiratory tract and an initial diagnosis of "grip" This picture has been emphasized by Blumer, by Ottenberg and Spiegel and by Rogers<sup>17</sup> Cameron and Ford stressed headache, anorexia and irritability There is abdominal discomfort, which may be so severe as to suggest acute appendicitis or biliary colic Constipation rather than diarrhea is the rule Fever usually is present

during the preicteric stage Leukopenia is the rule These prodromal symptoms tend to disappear after the onset of jaundice The liver usually is enlarged and tender Splenic enlargement is much less frequent The jaundice usually clears in one to four weeks

The epidemic of jaundice associated with the use of human serum in the preparation of yellow fever vaccine was discussed last year<sup>18</sup> These cases differed from those encountered in ordinary epidemics of infectious hepatitis in the long incubation period This varied from forty to one hundred twenty days but usually was between seventy and ninety days The gradual onset with less marked prodromal symptoms, the usual absence of fever and the normal leukocyte count seem further to differentiate this disease from the epidemic type of hepatitis

Detailed reports of this epidemic to date are limited in number One of the most extensive is that of Turner and his associates,<sup>19</sup> who studied 4,083 cases, with 14 deaths, occurring at Camp Polk, La In this group the incubation period varied from nine to twenty-three weeks The most common symptoms on the patients' admission were anorexia, weakness, nausea, abdominal pain and vomiting These often preceded the jaundice Fever was unusual

Jaundice and enlargement and tenderness of the liver were the most important findings on physical examination Evidences of a hemorrhagic diathesis were usual when the disease was severe Slight leukocytosis was the rule

The most important complications were as follows 1 Evidences of disturbances in the central nervous system appeared as changes in personality, delirium or severe coarse tremor of the extremities A restless stupor deepening into hepatic coma was seen in the fatal cases 2 Petechial hemorrhages in the skin and mucous

9 Hiscock, I V, and Rogers, O F Outbreak of Epidemic Jaundice Among College Students, *J A M A* **78** 488 (Feb 18) 1922

10 Blumer, G Infectious Jaundice in the United States, *J A M A* **81** 353 (Aug 4) 1923

11 Ford, J C Infective Hepatitis Three Hundred Cases in an Outer London Borough, *Lancet* **1** 675 (May 29) 1943

12 Evans, P Comments on Epidemic of Hepatitis, *Brit M J* **2** 446 (Oct 17) 1942

13 Leffkowitz, M, cited in Infectious Hepatitis in Palestine, *Foreign Letters (Palestine)*, *J A M A* **123** 1062 (Dec 18) 1943

14 Marchand, J F Tribal Epidemics in the Yukon, *J A M A* **123** 1019 (Dec 18) 1943

15 Willcox, W The Epidemic Jaundice of Campaigns, *Brit M J* **1** 297 (Feb 26) 1916

16 Cameron, J D S Infective Hepatitis, *Quart J Med* **12** 139 (July) 1943

17 Rogers, O F Epidemic Hepatitis, Correspondence, *J A M A* **123** 1066 (Dec 18) 1943

18 Greene, C H Liver and Biliary Tract A Review of the Literature for 1942, *Arch Int Med* **71** 563 (April) 1943 Jaundice Following Yellow Fever Vaccination, editorial, *J A M A* **119** 1110 (Aug 1) 1942 The Outbreak of Jaundice in the Army, *Medicine and the War*, *ibid* **120** 51 (Sept 5) 1942 Fox, J P, Manso, C, Penna, H A, and Madureira Para Observations on Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, *Am J Hyg* **36** 68 (July) 1942 Findlay, G M, and MacCallum, F O Hepatitis and Jaundice Associated with Immunization Against Certain Virus Diseases, *Proc Roy Soc Med* **31** 799 (May) 1938 Oliphant, J W, Gillian, A G, and Larson, C L Jaundice Following Administration of Human Serum, *Pub Health Rep* **58** 1233 (Aug 13) 1943

19 Turner, R H, Snavlev, J R, Grossman, E B, Buchanan, R N, and Foster, S O Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine, with Especial Consideration of Severe Attacks, *Ann Int Med* **20** 193 (Feb) 1944

membranes were the commonest complication. Massive gastrointestinal hemorrhage was also seen. The response of the blood prothrombin to treatment with vitamin K was one of the best guides to prognosis. 3 Ascites was reported in 13 cases and sometimes was associated with a high concentration of protein in the ascitic fluid. Turner and his associates expressed the opinion that capillary injury was of greater significance in the development of ascites than was reduction in the plasma protein, though this also showed changes. 4 Renal disturbances were manifested by albuminuria and a defective concentration of the urine. 5 Anemia, commonly macrocytic, was a frequent complication, which usually developed late in the course of the illness.

Turner and his associates pointed out that capillary hemorrhage was the most frequent complication in these cases. They concluded that the capillary hemorrhage together with congestion and stasis in the spleen and other viscera leads to increased hemolysis. The products of this hemolysis together with the products of lysis of damaged hepatic cells lead to disturbances in the functioning of the kidneys as well as of the remaining hepatic tissue. Such a process, in their opinion, explains many of the clinical manifestations reported.

Jaundice has developed after the use of human serum for other conditions. Probert<sup>20</sup> reported on a group of children who received pooled convalescent measles serum and in whom jaundice developed after seventy-eight to eighty-three days. Investigation by the British Ministry of Health<sup>21</sup> showed that 109 persons had been inoculated with this convalescent measles serum. Jaundice developed in 41, with few fatalities.

Jaundice has been reported to occur in soldiers after the prophylactic use of plasma from patients convalescent from mumps. This subject has been reviewed in detail in a report of the British Ministry of Health<sup>22</sup>. Reference was made there to 12 reported cases of jaundice in persons who had previously been given transfusions of plasma or of whole blood. Beeson<sup>23</sup> reported 7 cases of jaundice developing thirty-three to one hundred and nineteen days after transfusion of pooled

plasma or of citrated blood. Morgan and Williamson<sup>24</sup> followed up a series of 50 patients who had received serum or dried plasma. Jaundice developed in 9 of these patients (18 per cent) after forty-nine to one hundred and seven days. The extremely high incidence of jaundice in this series emphasizes the need for a careful and prolonged follow-up of patients receiving plasma or blood by transfusion.

In the past, attempts at experimental transmission of infectious hepatitis have been unsuccessful. Cameron<sup>16</sup> and Van Rooyen and Gordon<sup>25</sup> administered bile, gastric washings and blood from patients with jaundice by a variety of routes to a variety of animals without being able to reproduce the disease.

Lainer<sup>26</sup> administered blood or bile from patients with sporadic catarrhal jaundice to a series of 15 healthy subjects. No evidence of jaundice or of hepatitis appeared in any of them. Voegt<sup>27</sup> administered duodenal juice from a patient with epidemic hepatitis orally to each of 4 human volunteers. Serum, plasma or hemolyzed erythrocytes from patients were injected into 6 other volunteers. In 6 of these recipients subclinical icterus or other signs of hepatic impairment developed. Findlay and Martin<sup>28</sup> produced jaundice in 3 human volunteers by instilling into the nares nasal washings from patients in the preicteric or early icteric stage of jaundice following injection of yellow fever vaccine. Symptoms appeared in the volunteers after twenty-eight, thirty and forty days. A report<sup>29</sup> has also been made to the effect that a virus has been cultivated from the duodenal fluid of patients with epidemic hepatitis.

Andersen,<sup>30</sup> of Copenhagen, noted that epidemics of hepatitis, contrary to most epidemics, had a greater case incidence in country villages.

20 Probert, S. A. Hepatitis After Prophylactic Serum, *Brit M J* **2** 677 (Sept 24) 1938.

21 McNalty, A. S. Annual Report of the Chief Medical Officer, Ministry of Health, for the Year 1943, London, His Majesty's Stationery Office, 1938, p. 38.

22 Homologous Serum Jaundice, Memorandum Prepared by Medical Officers of the Ministry of Health, *Lancet* **1** 83 (Jan 16) 1943.

23 Beeson, P. B. Jaundice Occurring One to Four Months After Transfusion of Blood or Plasma. Report of Seven Cases, *J A M A* **121** 1332 (April 24) 1943.

24 Morgan, H. V., and Williamson, D. A. J. Jaundice Following Administration of Human Blood Products, *Brit M J* **1** 750 (June 19) 1943.

25 Van Rooyen, C. E., and Gordon, I. Some Experimental Work on Infective Hepatitis in M. E. F., *J Roy Army M Corps* **79** 213 (Nov) 1942.

26 Lainer, F. Zur Frage der Infektiosität des Ikterus, *Wien klin Wchnschr* **53** 601 (July 26) 1940.

27 Voegt, H. Zur Ätiologie der Hepatitis epidemica, *München med Wchnschr* **89** 76 (Jan 23) 1942.

28 Findlay, G. M., and Martin, N. H. Jaundice Following Yellow Fever Immunization. Transmission by Intranasal Instillation, *Lancet* **1** 678 (May 29) 1943.

29 Siede, W., and Luz, K. Zur Ätiologie der Hepatitis epidemica, *Klin Wchnschr* **22** 70 (Jan 23) 1943.

30 Andersen, T. T. Etiology of Hepatitis Epidemica (Epidemic Jaundice), *Acta med Scandinav* **93** 209, 1937. Andersen, T. T., and Tulinus, S. Etiology of Hepatitis Epidemica (Epidemic Jaundice), *ibid* **95** 497 1938.

than in urban communities. Jaundice occurs in epidemics in pigs, and he was able to transfer the disease of pigs through four generations in young pigs by feeding infected livers. He also produced jaundice in pigs by feeding 50 cc of duodenal bile from human patients with jaundice. The incubation period was short, only three to four days. Blumer<sup>31</sup> reported 2 cases of febrile jaundice occurring within five days after the patients had eaten roast pork.

It is generally accepted at the present time<sup>32</sup> that the infectious nature of epidemic hepatitis has been established. Experiments in its transmission suggest that it is due to a virus, while differences in the reported incubation periods and in the clinical pictures suggest that there are several viruses which may produce jaundice. The period of greatest infectivity apparently is during the prodromal and preicteric stages of the disease, and the infectivity may be lost shortly after clinical jaundice becomes manifest. Children are more susceptible than adults, and only a small proportion of the adults in an urban population are susceptible. Failure to recognize these relationships may be responsible for some of the difficulty in the experimental transmission of the disease.

Rapid, simple clinical methods for the recognition of these hepatotoxic viruses would do much to clarify the etiology and diagnosis of hepatitis and jaundice.

#### ASPIRATION BIOPSY OF THE LIVER

The study of specimens of liver obtained by the routine postmortem use of the viscerotome has been of great value in determining the incidence and extent of infection with yellow fever in South America.

Similar studies by Roholm and Iversen<sup>33</sup> by means of aspiration biopsy of the liver have done much to clear up the pathologic picture of acute hepatitis<sup>34</sup> "Catarrhal jaundice" as used by

Virchow<sup>35</sup> to indicate obstruction of the common duct in the course of a "duodenal catarrh," is now generally accepted as a misnomer. Opportunities for pathologic examination of the liver in cases of this condition have been few. In this country Klemperer, Killian and Heyd<sup>36</sup> were the first to emphasize the existence of parenchymal lesions in the liver. Barber and Osborn<sup>37</sup> and Findlay and Dunlop<sup>38</sup> have recently reported cases of simple jaundice in which they demonstrated the presence of acute necrosis of the liver.

Roholm and Iversen have made routine aspiration biopsies of the liver in a series of 26 cases of sporadic jaundice. They inserted a cannula into the liver in the right ninth interspace at the posterior axillary line. By means of a record syringe pieces of liver 1 to 2 cm long and 2 mm in diameter were aspirated. They found disarrangement of the hepatic cells with necrotic changes, especially in the centers of the lobules. There were mononuclear cell infiltration and increase of connective tissue around the portal spaces and in some of the lobules.

These studies of Roholm and Iversen have been extended by Dible, McMichael and Sherlock<sup>39</sup> in a series of 56 cases of acute hepatitis, 14 of them cases of epidemic hepatitis. The jaundice followed arsenotherapy in 35. In the remainder the jaundice followed prophylactic use of mumps convalescent serum or transfusion of serum. In all they found degenerative, necrotic or autolytic changes in the hepatic cells, especially in the center of the lobules. Repeating the biopsy after recovery showed that in some cases there was complete restitution and that in others acute or subacute necrosis (atrophy) or occasionally mild fibrosis or cirrhosis resulted. In no case was there evidence of bile stasis, which is claimed to occur in catarrhal jaundice. The lesions in the liver were similar in all the groups of cases studied, but this is not to be taken as proof of a common causation of the different types of jaundice.

31 Blumer, G. Note on Relationship Between Jaundice in Pigs and Jaundice in Human Beings, *J Mt Sinai Hosp* 8 418 (Jan-Feb) 1942.

32 Infective Hepatitis in the War, *Foreign Letters* (London), *J A M A* 121 879 (March 13) 1943. Catarrhal and Human Serum Jaundice, editorial, *ibid* 122 746 (July 10) 1943. Problem of Infectious Jaundice, editorial, *ibid* 122 1186 (Aug 21) 1943. Epidemic Hepatitis or Catarrhal Jaundice, editorial, *ibid* 123 636 (Nov 6) 1943. Dietrich, S. Der sogenannte katarrhalische Ikterus und die Hepatitis epidemica, *Deutsche med Wchnschr* 68 5 (Jan 2) 1942. Gutzeit, K. Ikterus infectiosus, *Munchen med Wchnschr* 89 185 (Feb 27) 1942.

33 Roholm, K., and Iversen, P. Changes in the Liver in Acute Epidemic Hepatitis (Catarrhal Jaundice) Based on Thirty-Eight Aspiration Biopsies, *Arch path et microbiol Scandinav* 16 427, 1939.

34 Problems of Infectious Jaundice, editorial, *J A M A* 122 1186 (Aug 21) 1943.

35 Virchow, R. Ueber das Vorkommen und den Nachweis des hepatogenen, insbesondere des katarrhalischen Icterus, *Virchows Arch f path Anat* 32 117, 1865.

36 Klemperer, P., Killian, J. A., and Heyd, C. G. The Pathology of "Ikterus Catarrhalis," *Arch Path* 2 631 (Nov) 1926.

37 Barber, H., and Osborn, G. R. Morbid Anatomy of Sporadic Cases of Infective Hepatic Jaundice, *J Path & Bact* 49 581 (Nov) 1939.

38 Findlay, G. M., and Dunlop, J. L. A Fatal Case of Acute Necrosis of the Liver Associated with Epidemic Catarrhal Jaundice, *Brit M J* 1 652 (April 9) 1932.

39 Dible, J. H., McMichael, J., and Sherlock, S. P. V. Pathology of Acute Hepatitis. Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice, *Lancet* 2 402 (Oct 2) 1943.



Roholm and Kiaup,<sup>40</sup> on the basis of clinical and biopsy studies, advanced the view that arsphenamine jaundice is nothing more than epidemic hepatitis in cases in which the resistance of the liver to the virus has been reduced by the arsphenamine. Similar views have been suggested by Bergstrand.<sup>41</sup> The relation of arsphenamine to hepatic disease and jaundice has been a debated topic for many years. Stokes, Ruedemann and Lemon<sup>42</sup> in 1920, for example, expressed views similar to those here reported. This question apparently will not be settled till it becomes possible to determine the role of virus infection in hepatic disease with assurance. The failure so far to isolate a virus from the liver in cases of epidemic jaundice or jaundice due to serum may be due to the fact that autopsy material has been used and that the virus has disappeared from the liver by the time of death. Watson<sup>43</sup> pointed out that aspiration biopsy early in the course of the disease may provide a means of recovering a virus.

Swedish investigators<sup>44</sup> have reported on aspiration biopsy in hundreds of cases and in a variety of hepatic diseases. They have insisted that it is a harmless procedure. Care must be taken in the selection of cases. The prothrombin time of the blood must be normal, to guard against postoperative hemorrhage. Complete biliary obstruction must be excluded, for injury to a bile duct in the presence of such obstruction may lead to the development of a biliary fistula. Cholangitis, hepatic abscess or other source of infection must be avoided. An improved biopsy needle has been reported by Tripoli and Fader.<sup>45</sup> Even under these conditions Watson reported that in many cases (40 per cent) it is difficult to obtain satisfactory specimens. Once this difficulty is surmounted it may be expected that hepatic biopsy will be more widely used in the future.

40 Roholm, K., and Krarup, N. B. Die Histopathologie der Leber bei sogenannten Salvarsanikterus mittels Aspirationsbiopsie untersucht, *Arch f Dermat u Syph* **181** 521, 1940.

41 Bergstrand, H. Ueber die akute und chronische gelbe Leberatrophie mit besonderer Berücksichtigung ihres epidemischen Auftretens in Schweden im Jahre 1927, Leipzig, Georg Thieme, 1930.

42 Stokes, J. H., Ruedemann, R. J., and Lemon, W. S. Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis, *Arch Int Med* **26** 251 (Nov.) 1920.

43 Watson, C. J. Personal communication to the author.

44 Iverson, P., and Roholm, K. On Aspiration Biopsy of the Liver, with Remarks on Its Clinical Significance, *Acta med Scandnav* **102** 1, 1939.

45 Tripoli, C. J., and Fader, D. E. The Differential Diagnosis of Certain Diseases of the Liver by Means of Punch Biopsy, *Am J Clin Path* **11** 516 (June) 1941.

#### LEPTOSPIRAL JAUNDICE (WEIL'S DISEASE)

In the first World War many cases of Weil's disease were described.<sup>46</sup> If trench warfare returns in the present conflict and troops again live in wet, rat-infested trenches, the number of cases of leptospiral jaundice will increase. Reports of such cases to date have been rare.<sup>47</sup>

Clapper and Meyers<sup>48</sup> reported 13 cases of Weil's disease in civilians and emphasized the clinical and laboratory evidence of meningitis and of cardiac damage present in addition to the jaundice and hepatic damage. Bruno, Wilen and Snavely<sup>49</sup> reviewed 15 cases observed in New Orleans between 1939 and 1941. They stressed the fact that the diagnosis is frequently missed and that the disease probably is much more common than indicated by published reports.

The clinical features of diagnostic significance are (1) an acute infectious disease with sudden onset, fever, headache and prostration, (2) severe myalgia appearing spontaneously or on pressure in the thighs, calves and back, (3) signs of hepatic damage, (4) signs of renal damage, (5) leukocytosis, (6) epidemiologic information as to exposure or occupation. The authors reemphasized that if any four of these features are present the diagnosis of Weil's disease should be considered.

Bruno and his associates stressed the meningeal and cardiac features seen in many cases. They pointed out that a hemorrhagic diathesis is present in many. This presumably is due to a toxic effect of the leptospires on the capillary wall, for normal prothrombin values were found in cases in which there were hemorrhagic changes. They also reported 4 cases in which bronchopulmonary features led to the condition's initially being mistaken for hepatitis secondary to pneumonia or resulting from treatment with a sulfonamide compound.

The diagnostic value of specific agglutinins against *Leptospira icterohaemorrhagiae* is generally recognized. Bruno and his associates reported 1 case in which the agglutinins in the blood were lost within three years after the patient's recovery. This is not necessarily the

46 Walch-Sorgdrager, B. Leptospiroses, *Bull Health Organ, League of Nations* **8** 143, 1939. Greene, C. H., and Farrell, E. Liver and Biliary Tract. A Review for 1939, *Arch Int Med* **65** 847 (April) 1940.

47 Varadi, S. Weil's Disease in an Army Camp. Case Report, *Brit M J* **1** 126 (Jan 30) 1943.

48 Clapper, M., and Meyers, G. B. Clinical Manifestations of Weil's Disease with Particular Reference to Meningitis, *Arch Int Med* **72** 18 (July) 1943.

49 Bruno, F. C., Wilen, C. J. W., and Snavely, J. R. Spirochaetal Jaundice. A Report on Fifteen Cases, Including Two Cases of *Leptospira Canicola* Infection, *J A M A* **123** 519 (Oct 30) 1943.

case, for Packchanian and Tom<sup>50</sup> reported 8 cases in which agglutinins were present in the blood from two to over twenty years after recovery from Weil's disease

Larson<sup>51</sup> reported the preparation of a specific immune serum which was of value in treating mice infected with Weil's disease. This serum was effective up to the third day of infection but was ineffective after the sixth day. More work must be done before the serum is available for clinical use. The need for early administration, moreover, will in many cases lessen its clinical usefulness

Of even greater interest is the report by Heilman and Herrell<sup>51a</sup> that penicillin is of value in the treatment of guinea pigs infected with Weil's disease

#### HEPATIC CIRRHOSIS IN MANSON'S SCHISTOSOMIASIS

Hepatic cirrhosis is the end result of infection with Manson's schistosomiasis. The clinical features of the condition have recently been reviewed by Koppisch<sup>52</sup> and Villela<sup>53</sup>. Koppisch pointed out that Manson's schistosomiasis is a disease of extended geographic distribution and of great importance as a cause of chronic illness and death within those regions. Africa, northern South America and the Caribbean region are the great endemic foci. In northern Africa it is found in the lower Nile Valley, particularly in the Delta, and in the Sudan. It is present along the East African coast from Zanzibar to below the Zambezi River. It occurs throughout parts of Tanganyika, the Belgian Congo and Rhodesia. In West Africa it is seen in Senegal and French Guinea. There is a small endemic focus in Yemen, Arabia. It was estimated in 1937 that in Egypt alone there were 3,000,000 cases of Manson's schistosomiasis.

In the New World it occurs in parts of northern and northeastern Brazil, with a variable incidence, which in one locality has reached 85.18

50 Packchanian, A., and Tom, N. Persistence of *Leptospira* Antibodies in Circulating Blood of Patients Recovered One to Over Twenty Years from Weil's Disease, *J Immunol* **46** 263 (May) 1943

51 Larson, C. L. Treatment of Young White Mice Infected with *Leptospira Icterohemorrhagiae* with Immune Serum, *Pub Health Rep* **58** 10 (Jan 1) 1943

51a Heilman, F. R., and Herrell, W. E. Penicillin in the Treatment of Experimental *Leptospirosis Icterohemorrhagica* (Weil's Disease), *Proc Staff Meet, Mayo Clinic* **19** 89 (Feb 23) 1944

52 Koppisch, E. Manson's Schistosomiasis, *J A M A* **121** 936 (March 20) 1943

53 Villela, E. Hepatic Lesions in Infections by *Schistosoma Mansoni*, *J A M A* **122** 690 (July 3) 1943, *Contribucao ao estudo histopatologico do figado no Schistosomose mansoni humana*, Hospital, Rio de Janeiro **23** 345 (March) 1943

per cent. In Venezuela its distribution seems to be restricted to a limited part of the north central zone, where 60 to 80 per cent of the population in the valleys near Caracas are infected. The disease is fairly common in Dutch Guiana. In Puerto Rico, 14.6 per cent of the autopsies performed in San Juan, a nonendemic center with a population of about 170,000, have shown evidences of the disease. Its incidence is greatest among persons in the second and third decades of life. It ordinarily affects members of the two sexes to about the same extent.

For the completion of the parasite's life cycle a specific intermediate molluscan host is necessary. Given suitable climatic and hydrographic conditions, a miracidium is hatched when the human feces containing ova of *Schistosoma mansoni* reach the water. It swims about until it finds a snail of the appropriate species, which it parasitizes. Within the snail the miracidium undergoes morphologic alterations and great multiplication, resulting, at the end of twenty-two to thirty-one days, in the emergence of large numbers of fork-tailed cercarias. The disease is acquired through exposure to cercarias, usually while a person is bathing in an infected stream or working in an irrigation canal, but infection can also take place through the buccal mucosa while one is drinking.

Spread of the disease can be avoided by (1) curing all who are affected with it so that no more viable ova will pass with their feces, (2) preventing the contamination of bodies of water with human excreta, (3) exterminating the snails or cercarias, and (4) keeping people away from the sources of infection. One or more or all of these methods may be applicable with success in a few communities, particularly in small ones, but in the larger endemic foci the density of the population and the extent of the infested territory make these methods impractical at the present time.

The usual route of penetration is through the skin. Since the metacercarias are next found in the lung, it is clear that in the derma they must enter either lymphatics or veins. In man they are supposed to enter the veins.

The course followed by the metacercarias seems at all times to be strictly intravascular. Those which are not caught and destroyed in the pulmonary circulation reach the left side of the heart, whence they are ejected with the arterial blood to all organs and tissues. Those which reach organs and tissues whose venous drainage is by way of the portal vein seem to be the only ones that survive and establish a foothold in the mammalian host. By passing from the arterial to the venous side in organs like

the spleen, pancreas, liver, stomach and small and large intestine, they reach intrahepatic portal branches, where they attain maturity

It is probable that in man most of the damage is accomplished by the ova. The characteristic mode of reaction of the tissues in all organs to the presence of these structures is by the formation of a pseudotubercle. The presence of ova leads to progressive fibrosis of portal spaces and of the submucosa of the colon, with ultimate development of a portal cirrhosis and splenomegaly if ova continue to be deposited in sufficient numbers over several years. As part of the cirrhosis there is portal obstruction, resulting in development of a collateral circulation, of which an important complication is the formation of esophageal varices that not infrequently give rise to fatal hemorrhage. The heightened blood pressure in the splenic vein favors the development of sclerotic changes in its wall, at times with calcification, and in a few cases thrombosis supervenes.

The manifestations of the disease, both clinical and anatomic, may conveniently be grouped into three stages: (1) an early period, comprising penetration of the cercarias, migration within blood vessels and maturation in intrahepatic portal branches, (2) an intermediate period, of progressive accumulation of ova in various organs and tissues, and (3) a late period, of frank visceral damage, mainly cirrhosis and splenomegaly.

In man this early period usually is asymptomatic, except for itching for a few hours over the parts exposed to the infested water. A history of well defined itching following a person's falling into, or bathing in, a stream should always bring to mind this disease, and if the stream is known to be infested such a history should be taken as strong presumptive evidence of infection's having actually taken place. Some patients complain of anorexia, weakness, loss of weight, headache, nausea, vague intestinal symptoms, looseness of the bowels and either feverishness or short accessions of high fever. These symptoms have their onset a few days to two weeks after exposure, and not all of them may be present at a given time. Unfortunately, these manifestations have so far been studied in but few cases, and, furthermore, it seems probable that they are present in the heavier infections only. Before ova begin to pass with the feces, there are no sure means of establishing the diagnosis.

The intermediate stage is taken to begin with the onset of oviposition, on or about the fortieth day after exposure. By this time wandering through the body has come to an end, and the

worms have reached maturity. The first well defined symptoms of this stage are accompanied by an abrupt onset with fever, accompanied or not by a chill, with a remittent or intermittent course and the temperature reaching 102 or even 104 F daily. The duration is at least two or three weeks, probably longer when not cut short by treatment with fuadin. The fever is accompanied by the usual symptoms of a febrile process, by generalized or localized abdominal discomfort, with or without pain, which may be colicky, by nausea, vomiting, abdominal distention, dysentery, urticaria and cough, which can be hacking and persistent. Physical examination may disclose patchy areas suggestive of bronchopneumonia and enlargement of the spleen and liver. There may be a severe eosinophilia with a low, normal or elevated leukocytic count.

Frequently there is nothing very characteristic about the disease during the early part of this stage, and the spleen and liver may not be palpable for a number of years after the onset. However given a case with the geographic possibility of infection, diarrhea with blood in the stools and obscure abdominal symptoms, this disease must be included in the differential diagnosis. In the earlier stages of the disease eosinophilia is frequent, and its presence is of great value in calling the observer's attention to a parasitic illness. Not enough emphasis can be laid on the importance of establishing the diagnosis at this stage, and the earlier the better. Failure to do this and to carry on treatment with fuadin will seal the patient's fate or condemn him to prolonged ill health.

In the late stage the clinical picture is dominated by the manifestations of cirrhosis with splenomegaly, ascites, anemia and cachexia. Diarrhea may still occur in bouts, but it may be absent for long periods. Vague abdominal symptoms and pain of variable intensity referred to some part of the colon usually persist. At any time during this stage there may come accessions of fever lasting from a few days to several weeks. Eosinophilia may persist in some cases, while in others it is lacking. Ova are often absent from the stools, mainly owing to the fact that the disease has lasted for many years and the number of ovipositing worms has become greatly reduced. The clinical picture may be the exact duplicate of Laennec's cirrhosis,<sup>53a</sup> or it may mimic the Banti syndrome when there is anemia.

53a Jaffe, R. Was lehrt uns die Bilharziazirrhose in bezug auf die Probleme der Leberzirrhose, *Schweiz med Wchnschr* 72 1149 (Oct 17) 1942, *General Considerations on Pathogenesis Syphilitic Aortitis, Myocarditis, Hepatic Cirrhosis*, *J Lab & Clin Med* 29 139 (Feb) 1944.

with leukopenia Hematemesis is of frequent occurrence and may be the first indication of cirrhosis, not infrequently it is the immediate cause of death The diagnosis at this stage depends on the clinical history, on the presence of eosinophilia, on repeated search for ova in the stools by means of methods of concentration and, lastly, on exploratory laparotomy with biopsy of the liver

Once cirrhosis is well developed, it is probable that the establishment of the diagnosis becomes of little more than academic interest Certainly, some symptoms, like those of colitis, may be favorably influenced by judicious treatment even in the presence of far advanced cirrhosis, but practically no effect will be exercised on the hepatic process, which will continue to progress relentlessly even after the parasites are destroyed

The liver may be large, small or of normal size It is always dense and pale, with a surface that is usually finely nodular and only exceptionally coarsely nodular On section the principal characteristic is the concentration of the fibrosis about the larger portal branches When this feature is well developed there are distinct collars of white or pink connective tissue about these veins—the so-called pipestem type of cirrhosis Microscopically, there is diffuse scarring of the portal spaces, with formation of pseudotubercles about ova, diffuse and focal infiltration with lymphocytes, plasma cells and eosinophils and more or less pigmentation of the Kupffer cells and phagocytes in the periportal tissues with finely divided brown pigment

The spleen may not be enlarged, even when there is advanced cirrhosis, but this is exceptional, splenomegaly being the rule In the late stage the spleen is characterized by a diffuse fibrosis of the pulp, which ultimately results in great reduction in the number of cells in the cords and a diminution in the size and number of lymphoid follicles Brown pigment is usually found in the reticuloendothelial cells of the organ

The ultimate cause of death is hematemesis due to a ruptured esophageal varix in one third of the advanced fatal cases, cachexia due to cirrhosis in another third and complications in the remainder The studies of Koppisch show that schistosomiasis is the cause of hepatic cirrhosis in fully one third of the cases encountered in Puerto Rico Because of the characteristic pathologic picture, aspiration biopsy, if feasible in such cases, would seem to be of value in differential diagnosis, as Villela has emphasized the importance of postmortem viscerotomy in the study of the epidemiology of this disease

#### AMEBIC HEPATITIS AND HEPATIC ABSCESS

Amebic dysentery is one of the most important of the tropical diseases which may be expected to be of military and postwar significance A discussion of amebic dysentery is without the scope of this review Its chief complication, amebic hepatitis and hepatic abscess, has been the subject of a comprehensive review by Ochsner and DeBaakey<sup>54</sup> In this monograph they present an analysis of 181 personal cases together with a review of the literature containing over 400 references

Ochsner and DeBaakey began by pointing out the fallacy in considering amebiasis a tropical disease *Endamoeba histolytica* is ubiquitous and has been found in all parts of the world While it has been generally accepted that 5 to 10 per cent of the population in this country harbor the parasite, recent surveys suggest that the true average incidence may be as high as 20 per cent

The incidence of hepatic complications in cases of intestinal amebiasis varies greatly, depending on the material studied According to Ochsner and DeBaakey it is approximately 4 to 5 per cent On the basis of these figures they calculated that 20,000,000 to 25,000,000 people in this country are infected with pathogenic amebas and that the potential number with hepatic complications is approximately 1,000,000 The importance of this problem, especially from the standpoint of public health, is obvious

Curiously, sex is an important factor in the development of this condition, for 83.9 per cent of patients with intestinal amebiasis are males, and 86.7 to 95.1 per cent of those in whom the hepatic complications develop are males Most of the patients were seen in the third, fourth and fifth decades of life

In the pathogenesis of amebic hepatitis it is agreed that amebas reach the liver from the primary focus in the intestine through the portal vein There they lodge in the smaller portal radicles, where they produce thrombosis with infarction and consequent focal necrosis These areas characteristically appear in the portal spaces and extend peripherally toward the capsule, thus paving the way for the cytolytic activity of the amebas to produce lysis and destruction of the involved hepatic parenchyma In this early phase of amebic hepatitis a balance exists between regression toward healing, with replacement by scar tissue, and progression toward supuration and abscess The balance between these

54 Ochsner, A., and DeBaakey, M. Amebic Hepatitis and Hepatic Abscess. An Analysis of One Hundred and Eighty-One Cases with Review of the Literature, *Surgery* 13 460 (March), 612 (April) 1943

two processes is determined by such predisposing factors as the relative resistance of the host and the virulence and number of the invading amebas. The presence of pathogenic bacteria, alcohol, trauma and other detrimental agencies also contributes to the formation of an abscess.

The typical abscess is filled with the characteristic chocolate sauce pus. Amebas may be found in the pus but are more frequently found in the cecum and ascending colon. Venous blood from this area drains through the superior mesenteric vein to the right lobe of the liver. This apparently explains why the majority of abscesses are single (65 to 88.6 per cent) and occur in the right lobe of the liver (84.7 to 96.3 per cent).

The clinical manifestations at the onset of hepatic abscess vary considerably. Usually they come on early, in the first three months of the course of an amebic dysentery, but may be acute, subacute or insidious in development. The most important systemic manifestation of hepatitis or abscess was fever, which usually was of low grade and intermittent. This was present in 84.5 per cent of the cases. Weakness, loss of weight, anorexia, diarrhea, chills and profuse perspiration, nausea and vomiting were less frequently observed. Jaundice was observed in 10.5 per cent of the cases. Diarrhea was present in 25.4 per cent of the cases, and a history of antecedent diarrhea could be obtained in only 67.2 per cent of these cases.

The earliest and most constant local manifestations of amebic hepatitis are pain and tenderness in the region of the liver. This was present in 86.7 per cent of the cases. Clinically recognizable enlargement of the liver was present in 72.9 per cent.

Laboratory findings include a moderate leukocytosis with an average count of 16,460 in this series. The majority of the patients showed a secondary anemia, which was more pronounced in those with chronic involvement. The frequency with which amebas are demonstrated in the stools varies with the technic of the examiner and the number of examinations made. Ochsner and DeBakey reported that amebas were found in 36.4 per cent of their cases.

Roentgenography is one of the most important and dependable laboratory procedures in the diagnosis of amebic abscess of the liver. The elevation and immobility of the diaphragm frequently are characteristic. In cases of uncomplicated abscess of the liver a distinct bulging of the diaphragm may be observed pointing upward into the lower pulmonary field in both the anteroposterior and the lateral roentgenograms. A positive diagnosis was made by roentgenography in from 69 to 100 per cent of the cases, depending

on the particular series reported. Ochsner and DeBakey reported a positive diagnosis in 88 per cent of their cases.

The diagnosis of amebic hepatitis and hepatic abscess is not difficult if the conditions are kept in mind and the clinical manifestations and results of laboratory examinations accorded due consideration. An amebic hepatitis should always be considered when a patient has low grade daily remittent or intermittent fever, pain and tenderness over the liver, moderate leukocytosis without a concomitant proportionate increase in polymorphonuclear leukocytes and *E. histolytica* in the stools. Such a clinical picture during or shortly after an attack of amebic dysentery more strongly indicates the presence of amebic hepatitis. However, it should be realized that even in the absence of intestinal manifestations the condition should be considered, repeated examinations of stools should be done and every attempt should be made to confirm or exclude the diagnosis of amebic hepatitis. The significance of early recognition of this condition has been emphasized repeatedly and lies in the fact that the institution of appropriate therapy during this presuppurative stage may prevent progression to abscess formation.

Whereas there is some variation in the clinical manifestations of amebic abscess of the liver depending on the chronicity of the process, persistent hepatomegaly, pain and tenderness over the hepatic area with occasional radiation to the shoulder, and a daily remittent or intermittent fever of moderate degree are fairly constant manifestations. The presence of these symptoms and signs should always suggest the possibility of an amebic abscess. Anorexia, loss of weight and strength, nausea and vomiting, profuse perspiration and disturbed slumber are less constantly observed, but their presence lends further support to the diagnosis. The presence of an antecedent dysentery is confirmatory evidence, but its absence is not refutatory. It will be recalled that from one third to almost one half of the patients gave no history of a previous dysentery. The diagnosis is supported further by a mild leukocytosis without a disproportionate increase in polymorphonuclear leukocytes. If, in addition to such a clinical picture the characteristic fluoroscopic and roentgenologic findings previously described are present, the diagnosis of amebic hepatic abscess is justified. The demonstration of active or encysted forms of *E. histolytica* is corroborative evidence, but their absence does not exclude the diagnosis.

It must be realized, of course, that whereas these findings justify the diagnosis of amebic hepatic abscess, its establishment depends on the



demonstration of the characteristic chocolate sauce pus. Herein lies the diagnostic importance of exploratory aspiration. However, the procedure should not be performed without thorough cognizance of its possible dangers. Of these the most important are (1) hemorrhage and (2) extension of infection. Various investigators have directed attention to the possibility of hemorrhage and have reported cases in which this dangerous complication followed exploratory aspiration of an amebic abscess of the liver. The danger of hemorrhage may be almost entirely avoided by administering emetine for several days preceding the aspiration and thus controlling the associated hepatitis. Extension of infection is another danger which deserves special consideration, since it is not always possible to determine clinically whether an amebic hepatic abscess is sterile or contains pyogenic organisms. The latter possibility should always be assumed and the aspiration performed in such a manner that an uninvolved portion of the peritoneum or the pleural cavity is not traversed by the aspirating needle. Obviously this is not always possible, but it should be kept in mind during the attempted aspiration. It should be realized also that this is not as difficult in the presence of an enlarged liver containing an abscess as under normal conditions, for with the former the anatomic relationships have been changed.

These hazardous possibilities, hemorrhage and extension of infection, may be avoided largely by preaspiration therapy with emetine, the type of needle employed, the technic of aspiration and the performance of the procedure in the operating room under absolutely aseptic precautions. Emetine hydrochloride should be administered for at least two to four days prior to aspiration in 1 gram (0.06 Gm.) doses daily. By employing a needle not longer than 10 cm. with a caliber not greater than 2 mm. the danger of puncturing a large vessel is minimized. Ochsner and DeBakey expressed preference for a short, beveled needle or a trocar type with a short, fairly blunt point. The procedure should always be performed in the operating room, first, because aseptic precautions are likely to be greater and, second, because if the abscess is found to be secondarily infected open drainage can be done immediately. The latter possibility can be readily determined by making an immediate smear of the aspirated pus, which will reveal on microscopic examination the presence of large numbers of bacteria and leukocytes in cases in which secondary infection is present. Whereas general anesthesia can be employed, local infiltration analgesia with 1 per cent procaine hydrochloride solution is preferable. Nicking the skin at the

contemplated site of puncture with a bistoury will facilitate insertion of the needle.

The cutaneous site of puncture and the direction of the introduction of the needle depend largely on the clinical and roentgenologic findings. Accordingly, in the presence of localizing signs and pointing of the abscess the needle should be introduced directly over the mass or at the site of greatest tenderness. However, if no localizing signs are present the roentgenograms may be of guiding significance. Thus in a case in which the lateral roentgenogram demonstrates the abscess in the anterior portion of the liver the needle may be inserted just below the anterior costal margin about 5 to 6 cm. lateral to the midline and directed superiorly and posteriorly. On the other hand, if the lateral roentgenogram reveals posterior localization of the abscess the needle should be introduced below the costophrenic angle and directed superiorly and anteriorly. However, in those cases in which the abscess is located more anteriorly near the dome of the liver, as occurs most frequently, avoidance of the pleural and peritoneal cavities may be accomplished best by inserting the needle in the ninth or tenth intercostal space in the anterior axillary line and directing it superiorly, medially and slightly posteriorly. Occasionally it may be necessary to puncture the liver in several different directions before pus is encountered. If multiple punctures are necessary it is extremely important to remove the needle entirely before reintroducing it in a different direction rather than changing its direction while the needle is still at its original site. In this way extensive injury to the friable parenchyma of the liver may be prevented. Yater<sup>55</sup> has emphasized the value of hepatosplenography with colloidal thorium dioxide when an abscess in the liver cannot be localized by ordinary roentgenograms.

The treatment of hepatic abscess in the past may be divided into three main periods. 1 The first was the period of purely medical treatment, during which evacuation of the purulent collection was allowed to take place spontaneously. The mortality during this period, which embraced the history of medicine up to the sixth decade of the eighteenth century, was 80 per cent. 2 The second epoch may be said to be limited to the short period from 1860 to the early 1870's, during which early exploration with the aspirator gradually

55 Meredith, R. H., Cooper, L. F., and Yater, W. M. Thorotrast Hepatosplenography as Diagnostic Aid in Solitary Liver Abscess. Report of Four Cases, *M. Ann. District of Columbia* 11:382 (Oct.) 1942. Yater, W. M., and Coe, F. O. Ten Years' Experience with Thorotrast Hepatosplenography, *Ann. Int. Med.* 18:350 (March) 1943.



became the rule of practice, to be followed by repeated explorations and finally cautious opening with trocars or caustic pastes or by means of small incisions. 3 The third period begins with the 1870's, when the Listerian discovery made surgeons bolder in opening the peritoneal and pleural cavities in an effort to evacuate the abscess early. During this period the trocar gradually yielded to the knife and the rule of surgical practice consisted of immediate evacuation by free incision regardless of situation or quantity of pus. That the mortality during this period was still extremely high is shown by the report on 182 patients admitted to the Charity Hospital in New Orleans during the ten year period 1884 to 1894, among whom there were 87 (or 42.56 per cent) deaths. 4 The combination of treatment with emetine plus aspiration may be considered as inaugurating the fourth, and most important, period in the treatment of amebic hepatitis and hepatic abscess.

Emetine is preferably administered subcutaneously as emetine hydrochloride in daily doses of 0.065 Gm (1 grain) until 0.39 to 0.65 Gm (6 to 10 grains) has been given. Because of its toxicity in excessive dosages and its cumulative action the noxious effects of this drug should be realized and considerable care exercised in its use. Experimental investigators have shown that it is essentially a protoplasmic poison with an apparent selective action on muscle. The danger of administering the drug in excessive dosage or over prolonged periods is indicated by the pronounced degenerative changes produced in the cardiac musculature. Clinical manifestations of its toxicity consist of severe diarrhea, nausea and vomiting, profound prostration, cardiac arrhythmia and failure, muscular pains and weakness, especially in the extremities. The maximum amount of emetine that should be given over any period of time should not exceed 10 mg ( $\frac{1}{6}$  grain) of emetine hydrochloride per kilogram of body weight. Accordingly, for a patient weighing 150 pounds (about 68 Kg) this would be about 0.65 Gm (10 grains). Other amebicides, such as acetarsone, carbarsone, treparsol (the sodium salt of 3-formylamino-4-oxyphenylarsinic acid) chiniofon, vioform, and diodoquin (5,7-diiodo-8-hydroxyquinoline), which are safer and more efficient in the treatment of intestinal amebiasis, are not considered desirable in the treatment of amebic hepatitis and hepatic abscess because they are not as effective in these conditions as emetine and because they are toxic to the liver. However, immediately after completion of therapy of the hepatic condition the patient should be given a course of therapy for the intestinal

amebiasis. While this frequently cannot be demonstrated clinically, it should be assumed to exist once the diagnosis of amebic hepatitis and hepatic abscess has been established. Moreover, the therapy employed for the latter should not be considered adequate for the treatment of the intestinal infestation. For this reason a separate and different type of therapy should be employed for the intestinal amebiasis.

Aspiration is the procedure of choice in cases in which evacuation of the abscess becomes necessary. In such cases, however, it should be realized that the preliminary administration of emetine is important. In the Tulane surgical service, emetine hydrochloride is administered routinely in daily doses of 0.065 Gm (1 grain) for two or four days preceding the aspiration. Because the majority of amebic abscesses of the liver are sterile and because of the prognostic and therapeutic importance of this fact, every attempt should be made to maintain this sterility. The evacuation of such an abscess by open drainage is invariably followed by secondary infection, and the morbid consequences of this development have been previously emphasized. It is possible to evacuate the abscess and simultaneously maintain its sterility only by closed drainage. In the series of Ochsner and DeBaakey open drainage was used in 80 cases, with a mortality of 22.1 per cent, and conservative therapy in 83, with 3 deaths, a mortality of only 3.6 per cent. Aspiration was performed without preliminary administration of emetine in 2 of these fatal cases, and within a relatively short period following the procedure manifestations of shock developed and the patients died. The other patient was treated with emetine and chiniofon by the medical service for almost three weeks, and no attempt was made to drain the hepatic abscess. At autopsy a huge hepatic abscess, measuring approximately 20 cm in diameter, was found, in addition to several smaller abscesses. Ochsner and DeBaakey expressed the firm conviction that these 3 tragedies could have been averted, the first 2 by preliminary administration of emetine and the third by aspiration of the abscess in addition to the use of emetine.

As previously emphasized, the procedure of aspiration should be performed in the operating room because the facility and reliability of strict asepsis are probably greater and because open drainage can be done immediately if the abscess is found to be secondarily infected. This may be determined readily by an immediate smear of the aspirated pus, which in cases of secondary infection would reveal on microscopic examination the presence of large numbers of bacteria.

and leukocytes. The technic of aspiration has been described, and the procedure is performed in a similar manner for both diagnostic and therapeutic purposes. The administration of emetine should be continued after closed drainage of the abscess until 0.39 to 0.65 Gm (6 to 10 grains) has been given. It is considered unnecessary as well as undesirable to introduce any substance into the abscess cavity, as the use of irrigating solutions of amebicides has been found to be valueless.

This last statement of Ochsner and DeBaakey summarizes past experience in the treatment of amebic abscesses of the liver which have become secondarily infected. Recently Noth and Hirshfeld<sup>56</sup> reported the aspiration of such an amebic abscess that was infected with beta hemolytic streptococci of group G. They inserted a small ureteral catheter through the aspirating needle and used it to inject penicillin into the cavity of the abscess. Twenty-five thousand units of penicillin was injected every four hours for eight doses. The dose was then progressively decreased to 5,000 units every four hours. Injections of penicillin were maintained for fifteen and a half days, and a total of 830,000 units was administered. With this treatment the patient became afebrile and asymptomatic and recovery was uneventful.

#### HEPATIC DAMAGE FROM TANNIC ACID

One of the important medical problems of the war has been the treatment of burns. Several papers, including those of Wilson, Macgregor and Stewart<sup>57</sup> and McClure and Lam,<sup>58</sup> have called attention to the importance of hepatic necrosis in cases of severe burns. Jaundice is of bad prognostic omen in such cases. Wells, Humphrey and Coll<sup>59</sup> were the first to incriminate the then popular tannic acid therapy as the causative agent in the hepatic necrosis.

Patients treated with tannic acid had marked elevation of the icterus index, decreased plasma prothrombin and strongly positive reactions to

cephalin flocculation tests. These tests of hepatic function elicited a normal response in patients treated with plain petrolatum.

Several investigators studied the problem experimentally. Forbes and Evans<sup>60</sup> showed that subcutaneous administration of tannic acid to rats resulted in hepatic necrosis. Cameron, Milton and Allen<sup>61</sup> found that tannic acid had an injurious effect on the livers of a variety of experimental animals and were able to demonstrate the absorption of tannic acid from burnt surfaces. Clark and Rossiter<sup>62</sup> showed that, in addition to the microscopic evidence of hepatic necrosis, functional impairment could be demonstrated by galactose tolerance tests. Additional detailed and confirmatory studies showing the poisonous effect of tannic acid on the liver and the changes in that organ after treatment of experimental burns with tannic acid have been reported by Hartman and Romence<sup>63</sup> and by Baker and Handler<sup>64</sup>.

The present consensus<sup>65</sup> is that the use of petrolatum or boric ointment gauze in the treatment of severe burns is preferable to application of tannic acid or other coagulation methods.

#### INDUSTRIAL POISONS AND DAMAGE TO THE LIVER

Numerous chemicals used in industry have a toxic effect on the liver. These have been discussed by Ottenberg and Spiegel. The exigencies of war cause a demand for numerous chemicals not commonly used in civilian industry.

Trinitrotoluene is one of the outstanding compounds in this class. During the last war it, together with the closely related nitrophenols (trinitrophenol [picric acid], etc.), was responsible for a great many cases of industrial poisoning and of toxic jaundice.<sup>66</sup> Evans<sup>67</sup> has

60 Forbes, J. C., and Evans, E. I. Tannic Acid and Liver Necrosis, *Surg., Gynec. & Obst.* **76** 612 (May) 1943.

61 Cameron, G. R., Milton, R. F., and Allen, J. W. Toxicity of Tannic Acid. Experimental Investigation, *Lancet* **2** 179 (Aug. 14) 1943.

62 Barnes, J. M., and Rossiter, R. J. Toxicity of Tannic Acid, *Lancet* **2** 218 (Aug. 21) 1943. Clark, E. J., and Rossiter, R. J. Liver Function in Rabbits After Injection of Tannic Acid, *ibid.* **2** 222 (Aug. 21) 1943.

63 Hartman, F. W., and Romence, H. L. Liver Necrosis in Burns, *Ann. Surg.* **118** 402 (Sept.) 1943.

64 Baker, R. D., and Handler, P. Animal Experiments with Tannic Acid, *Ann. Surg.* **118** 417 (Sept.) 1943.

65 McClure, R. D. Personal communication to the author.

66 Voegtlin, C., Hooper, C. W., and Johnson, J. M. Trinitrotoluene Poisoning. Its Nature, Diagnosis and Prevention, *Hygienic Laboratory Bulletin* 126, United States Treasury Department, Public Health Service,

56 Noth, P. H., and Hirshfeld, J. W. Amebic Abscess of the Liver with Secondary Infection. Local Treatment with Penicillin, *J. A. M. A.* **124** 643 (March 4) 1944.

57 Wilson, W. C., Macgregor, A. R., and Stewart, C. P. Clinical Course and Pathology of Burns and Scalds Under Modern Methods of Treatment, *Brit. J. Surg.* **25** 826 (April) 1938.

58 McClure, R. D., and Lam, C. R. Problems in Treatment of Burns. Liver Necrosis as Lethal Factor, *South. Surgeon* **9** 223 (April) 1940.

59 Wells, D. B., Humphrey, H. D., and Coll, I. J. Relation of Tannic Acid to Liver Necrosis Occurring in Burns, *New England J. Med.* **226** 629 (April 16) 1942.

reported 7 cases of toxic necrosis of the liver with jaundice, with 2 fatalities, in British munition workers Palmer, McShane and Lipman<sup>68</sup> reported 3 cases, with recovery in all. The jaundice came on suddenly and insidiously. Anorexia, nausea, vomiting and epigastric distress sometimes preceded the jaundice but sometimes appeared at the same time.

All the studies dealing with trinitrotoluene poisoning<sup>69</sup> have emphasized the importance of prevention of this disease by careful selection of workers and constant supervision of the conditions of their employment. The last include wearing of freshly laundered uniforms, an obligatory shower bath at the end of the work period, improved ventilation and use of respirators in some situations. Even with care there still may be excessive exposure to dust and fumes. The difference between the numbers of cases of poisoning reported at the present time and those reported during the past war is a measure of the value of these preventive measures.

Chlorinated hydrocarbons produced chemically by the chlorination of naphthalene and diphenyl and known by the trade name of Halowax are used extensively in the insulation of certain types of electrical cables. Workers handling Halowax acquired a characteristic type of dermatitis, which was described in Germany in 1927<sup>70</sup> and by Schwartz<sup>71</sup> in this country.

Since the war a great deal of Halowax has been used in the manufacture of special electrical

cables used on shipboard. Good and Pensky<sup>72</sup> have reviewed the extensive literature dealing with Halowax acne or "cable rash" that has appeared in consequence. The patients seen by Good and Pensky were exposed primarily to dust, and only a dermatitis developed. They encountered no cases of jaundice, and tests of hepatic function gave normal results. Schwartz<sup>73</sup> pointed out that jaundice and damage to the liver do occur among workers exposed to fumes of Halowax, but detailed reports are not yet available on cases of jaundice following poisoning by Halowax. I have encountered a number of such cases, and the clinical picture is that of an acute or subacute toxic jaundice, which may develop insidiously. Again the importance of preventive measures must be emphasized.

Tetrachlorethane is another toxic organic solvent which has been extensively used in industry during the war. Gurney<sup>74</sup> has described the medical measures taken in one plant to further the early recognition or prevention of poisoning and hepatic damage. Of a group of 277 employees, 75, or 27.1 per cent, had such symptoms or complaints as headache, giddiness, anorexia and nausea associated with exposure to the fumes of tetrachlorethane. Fifty-five, or 19.8 per cent, of these employees had enlargement of the liver. Only 6 had sufficient hepatic damage to produce clinical jaundice. Clinical recovery was prompt in all patients on removal from exposure to the gas and on standard treatment. Gurney stressed (1) hygienic and preventive measures for reducing the exposure to toxic materials, (2) frequent physical examination, with emphasis on the size of the liver and clinical evidence of jaundice, and (3) widespread use of a few simple laboratory tests for hepatic injury. The laboratory tests were selected for their ease of application to large numbers of employees. That the tests took a minimum of the employees' time and required no special preparation and could be done with limited laboratory equipment were the chief factors in their selection. The tests used were those for bile and urobilinogen in the urine and determination of the icterus index and the cephalin flocculation test of the

1920 Discussion on the Origin, Symptoms, Pathology, Treatment and Prophylaxis of Toxic Jaundice Observed in Munition Workers, *Proc Roy Soc Med* **10** 106 (Jan) 1917

67 Evans, R. M. TNT Jaundice, *Lancet* **2** 552 (Nov 8) 1941

68 Palmer, W. L., McShane, G. S., and Lipman, W. H. Toxic Necrosis of the Liver from Trinitrotoluene! Report of Three Cases, *J A M A* **123** 1025 (Dec 18) 1943

69 Roberts, H. M. The TNT Health Hazard, *Brit M J* **2** 647 (Nov 8) 1941. Preventive Work in Connection with TNT Poisoning, *Bull War Med* **2** 526 (July) 1942. Discussion on Trinitrotoluene Poisoning, *Proc Roy Soc Med* **35** 553 (June) 1942. von Oettingen, W. F. The Aromatic Amino and Nitro Compounds. Their Toxicity and Potential Dangers, *Public Health Bulletin* 271, Federal Security Agency, United States Public Health Service, 1941

70 Teleky, L. Die Pernakrankheit (Chloracne), *Klin Wchnschr* **6** 845 (April 30), 897 (May 7) 1927. Koelsch, F., in Ullmann, K., Oppenheim, M., and Rille, J. H. Die Schädigungen der Haut durch Beruf und gewerbliche Arbeit, Leipzig, Leopold Voss, 1926, pp 303-343

71 Schwartz, L. Dermatitis from Synthetic Resins and Waxes, *Am J Pub Health* **26** 586 (June) 1936, *Skin Hazards in American Industry* Part II, *Public Health Bulletin* 229, United States Treasury Department, Public Health Service, 1936

72 Good, C. K., and Pensky, N. Halowax Acne ("Cable Rash") A Cutaneous Eruption in Marine Electricians Due to Certain Chlorinated Naphthalenes and Diphenyls, *Arch Dermat & Syph* **48** 247 (Sept) 1943

73 Schwartz, L. An Outbreak of Halowax Acne ("Cable Rash") Among Electricians, *J A M A* **122** 158 (May 15) 1943, footnote 71

74 Gurney, R. Tetrachlorethane Intoxication. Early Recognition of Liver Damage and Means of Prevention, *Gastroenterology* **1** 1112 (Dec) 1943

serum My personal experience has confirmed the report of Gurney as to the usefulness of these tests in selecting patients for intensive study

#### INTESTINAL OBSTRUCTION FROM GALLSTONES

Intestinal obstruction from gallstones has been the subject of comprehensive reviews by Foss and Summers<sup>75</sup> and Hinchey<sup>76</sup> The spontaneous formation of a fistulous opening between the gallbladder and some portion of the intestinal canal is not an infrequent complication of cholecystitis, though statistical studies of its exact frequency are not available When such an internal biliary fistula forms, any gallstones present in the gallbladder tend to be evacuated into the bowel In 176 cases of cholecystoenteric fistula studied by Wakefield, Vickers and Walters<sup>77</sup> gallstones produced an intestinal obstruction in but 10 According to Foss and Summers,<sup>75</sup> this accident happened in only 0.3 per cent of the cases of disease of the gallbladder and bile ducts which had been observed by him Other reports in the literature indicate that gallstones are responsible for from 1 to 6 per cent of cases of intestinal obstruction Hand and Gilmore<sup>78</sup> collected reports of 12,153 cases of intestinal obstruction from the literature and found that gallstones were responsible for the obstruction in 208 cases, or 1.7 per cent

Such cases are being recognized with increasing frequency, for von Wagner<sup>79</sup> in 1914 reported finding 334 cases in the literature Moore<sup>80</sup> in 1925 reported 400 cases, while Foss and Summers<sup>75</sup> collected records of 140 other cases reported since then The symptoms are variable From 46<sup>75</sup> to 50<sup>76</sup> per cent of the patients give a history indicative of chronic disease of the gallbladder or suggestive of biliary colic In 15 per cent of the cases reported by Foss the patients gave no history of previous ill health or indigestion Approximately one third (32 per cent) give a history of an attack of epigastric pain sufficiently different from the previous biliary colic that it could be ascribed

to perforation of the gallbladder or to passage of stones into the intestine

Once in the intestine, small stones pass through the bowel and are evacuated without further incident Stones large enough to produce ileus produce variable symptoms, depending on the site of the obstruction Foss and Summers<sup>75</sup> reported that in 83 per cent of their cases with ileus the stone had lodged in the ileum and in 59 per cent it was in the terminal portion of the ileum, i. e., within 12 inches (30 cm) of the ileocecal valve According to Hinchey, 50 per cent of the patients give a recurrent history of obstructive symptoms, apparently associated with passage of the stone along the intestine

The preoperative diagnosis is greatly facilitated by proper roentgenologic examination Rigler, Borman and Noble<sup>81</sup> stressed the importance of (1) roentgenologic evidence of obstruction as demonstrated by scout films of the abdomen and (2) direct visualization of the stone, though, as Hinchey observed, it may be seen but is not always identified as a gallstone If a Miller-Abbott tube has been passed successfully to deflate the obstructed bowel, the introduction of a small amount of thin barium sulfate solution may delineate the impacted stone This is a safer diagnostic procedure than is the oral administration of barium sulfate The demonstration of a cholecystoenteric fistula likewise is a valuable confirmatory sign in a case suspected to be one of intestinal obstruction due to gallstones The biliary radicles may be outlined by gas in the ducts, or the fistula and biliary tree may be outlined by the regurgitation of barium sulfate from the intestinal canal

Treatment is primarily surgical Wangenstein<sup>82</sup> and Owens<sup>83</sup> reported cases in which decompression of the bowel with a Miller-Abbott tube relieved the symptoms of obstruction and the gallstone was passed by rectum shortly thereafter This fortunate response is not the rule, for Hinchey and Hand reported cases in which the obstruction was not relieved by intubation

Many of the patients are advanced in years, the average age in different series varying from 62 to 66 In a large proportion of cases either

75 Foss, H. L., and Summers, J. D. Intestinal Obstruction from Gall Stones, *Ann Surg* **115** 721 (May) 1942

76 Hinchey, P. R. Gallstone Ileus, *Arch Surg* **46** 9 (Jan) 1943

77 Wakefield, E. G., Vickers, P. M., and Walters, W. Intestinal Obstruction Caused by Gallstones, *Surgery* **5** 670 (May) 1939

78 Hand, B. H., and Gilmore, W. E. Gallstone Ileus, *Am J Surg* **59** 72 (Jan) 1943

79 Wagner, A. Ileus durch Gallensteine, *Deutsche Ztschr f Chir* **130** 353, 1914

80 Moore, G. A. Gallstone Ileus, *Boston M & S J* **192** 1051 (May 28) 1925

81 Rigler, L. G., Borman, C. N., and Noble, J. F. Gallstone Obstruction, *J A M A* **117** 1753 (Nov 22) 1941

82 Wangenstein, O. H. The Therapeutic Problem in Bowel Obstruction. A Physiological and Clinical Consideration, Springfield, Ill., Charles C. Thomas, Publisher, 1937

83 Owens, F. M., Jr. Gallstone Ileus. Successful Treatment with Miller-Abbott Tube, *Gastroenterology* **1** 938 (Oct) 1943

the diagnosis is not made or the decision to operate is reached only after a considerable delay. It therefore is not surprising that the operative mortality is about 50 per cent.

Early diagnosis and prompt surgical intervention give the greatest promise for a reduction in mortality. Search should always be made for further stones in the bowel, for numerous cases have been reported of recurrent obstruction from multiple gallstones in the intestine. It is still too soon to tell if the present vogue for the use of sulfanilamide crystals in the peritoneal cavity will reduce the operative mortality in cases of this type. Mastin<sup>84</sup> made the worthwhile suggestion that the risk of peritonitis from

leakage of the suture line in the ileum may be obviated by delivering the loop of ileum containing the gallstone outside the abdomen and maintaining this exteriorization until the danger of leakage from the suture line is past.

The management of the biliary fistula should be regarded as a separate surgical problem from the relief of the intestinal obstruction. A cholecystocolic fistula is particularly likely to give rise to cholangitis, and its early closure is advocated.<sup>77</sup> When the biliary fistula is to the stomach, duodenum or jejunum, it is agreed that intervention frequently is unnecessary.

In the long run, earlier recognition of gallstones and removal of them before they have an opportunity to perforate into the intestine perhaps offer the greatest hope of reducing the danger of gallstone ileus.

<sup>84</sup> Mastin, E. V., in discussion on Foss and Summers.<sup>75</sup>

## Book Reviews

**Gastro-Enterology** By Henry L Bockus, M D  
Volume II Price, 3 volumes and separate desk index, \$35 Pp 975, with 176 illustrations, 12 in colors Philadelphia and London W B Saunders Company, 1944

This book is the second of a series of three volumes on gastroenterology prepared by a recognized authority in the field, who also is one of the outstanding teachers of modern medicine

The volume begins with section IV of the series. The section is on diseases of the small intestine and consists of fifteen chapters. This section is followed by section V, on diseases of the colon, which consists of twenty chapters. The final section of the volume, section VI, deals with diseases of the peritoneum, mesentery and omentum and is divided into two chapters

The section on the small intestine includes, in part, discussions of the clinical approach to the study of diseases of the mesenteric small intestine, embryology and anomalies, duodenal stasis, duodenitis, duodenal parasites, duodenal fistulas and other injuries, diverticulosis, tumors, regional enteritis, tuberculosis and idiopathic steatorrhea, and an excellent chapter on intestinal obstruction

Under diseases of the colon, methods of study and examination based on the rich clinical experience of the author are outlined. The chapter on functional disorders of the colon is especially enlightening, and this difficult problem is dealt with in a sound and practical manner. The chapters on megacolon, melanosis and foreign bodies are instructive. The discussions of amebiasis and bacillary dysentery admirably set forth modern views and the best current treatment of these conditions. The book contains a long and detailed chapter on ulcerative colitis, in which the views of many contemporary workers are discussed. Perhaps too much space is devoted to the opinions of others in the discussion of causation of this group of infections. The reader would do well in reading this chapter to keep in mind that the discussion concerns itself with several disease entities, and to try to evaluate the author's views concerning them. The information gleaned in this way may be controversial, but it represents the latest published thought on the subject

The first of the two chapters of section VI is concerned with the nature and structure of the peritoneum and with tumors and inflammations of the peritoneum and their treatment, as well as with evaluation of, and the technic of, peritoneoscopy. The second of the two chapters is concerned with the omentum and mesentery

The entire volume offers highly instructive reading and leaves the reader with the thought that the task has been well done. It will serve as a useful reference volume for many years to come

**Osler's Principles and Practice of Medicine**  
Edited by Henry A Christian, A M, M D, L L D (Hon), Sc D, Hon F R C P (Can), F A C P  
Fifteenth Edition Price, \$9.50 Pp 1498 New York and London A Appleton-Century Company, Inc, 1944

Only eighteen months after the fourteenth, or semi-centennial, edition of this classic medical text, a fifteenth edition appears. This achievement is especially note-

worthy when one considers the difficulty in obtaining material and labor during these war years and is first hand evidence of the demand of students and practitioners for the work

This text by a single author is 1,498 pages in length, including a most detailed index, and adheres closely to the arrangement of the fourteenth edition. Scattered throughout the book one finds instances in which additions have been interpolated. For example, page 361 (1) deals with ornithosis, while page 361 (2) treats of phlebotomus fever. The indications for use of some of the newer drugs are mentioned in detail, as for example, penicillin and totaquine, and an up-to-date bibliography on these recent advances in medicine leaves little to be wished

As a whole, the contents are so impressively handled that one is inclined to overlook the sketchy covering of some subjects, such as hemoglobinuria. The reviewer is impressed with the number of the rarer ills of man which the editor has contrived to include in this book

The only real fault to be found is the manner of presenting the references. It would facilitate reading greatly to have them listed

**Plants and Vitamins** By W H Schopfer Authorized translation by N L Noecker Foreword by W J Robbins Price, \$4.75 Pp XIV and 293 Waltham, Mass Chronica Botanica Company, 1943

This book summarizes the present knowledge of vitamins in plants. The literature up to 1941 is reviewed fairly completely, and problems for future investigation are pointed out. As the author indicates, the volume shows only a stage of progress in research which continues to advance. Much of the material discussed is based on contributions of the author, who pioneered in this field and whose work has stimulated many subsequent investigations

The book contains twenty-four chapters and is divided into three parts. Part I deals with the synthesis of vitamins in plants, auxoautotrophic plants and research methods. In part II vitamins are discussed in relation to plants unable to synthesize them and considerable emphasis is given to growth factors of micro-organisms. Part III is concerned with general problems involving vitamins

This book will be of interest primarily to animal and plant physiologists and to a lesser extent to others engaged in vitamin research, especially workers whose investigations involve bioassays with micro-organisms

**Allergy in Practice** By Samuel L Feinberg Price, \$8 Pp 798 Chicago The Year Book Publishers, Inc, 1944

In his introduction the writer states that he has tried to reach a middle ground between the elementary sketch of the subject and the "elaborate, unwieldy, cumbersome and often encyclopedic tome." At any rate he has produced an excellent book, clearly and concisely written and thoroughly documented with many references to the literature. The subject is covered, however, in the conventional manner, and, while the material is well up to date, there is nothing of startling novelty. The tables and illustrations are useful and the index is comprehensive



## BAGASSE DISEASE OF THE LUNGS

W A SODEMAN, MD, AND R L PULLEN, MD  
NEW ORLEANS

Bagasse is the product remaining after extraction of sugar from sugar cane. This material is commonly baled and if not used immediately may remain exposed in the field for some months before being converted, by processing, into insulating and acoustic board. Workers employed in the breaking of these bales sometimes acquire a respiratory illness. Seven cases of such a reaction have been reported.<sup>1</sup> In order to clarify the clinical picture and course of this disturbance, we are summarizing, aside from the 7 reported cases, 11 of our own. The following 2 histories are given in detail to bring out some of the difficulties in the evaluation of possible etiologic factors.

### REPORT OF CASES

**CASE 1**—J N, a white youth aged 18, entered the hospital on Oct 2, 1942, complaining of shortness of breath of one week's duration. He had been working for one month in an industrial plant handling bales of bagasse. The onset of the shortness of breath was acute, but the patient continued to work that day and the following day, finally being forced to rest by the progressively more severe dyspnea. There was a slight cough producing mucoid sputum. No hemoptysis was noted. The systemic review revealed nothing of note. At the time of his admission the temperature was 100.6 F, the pulse rate 112 per minute, the respiratory rate 56 per minute and the blood pressure 120 systolic and 70 diastolic. Aside from the profound dyspnea, the patient did not appear acutely ill. The chief physical findings were limited to the chest and were as follows: unimpaired respiratory excursion and motion, unimpaired tactile and vocal fremitus, normal resonance and bronchovesicular to bronchial breathing over the lower left quadrant of the chest posteriorly. No rales or rubs were heard.

An examination of the blood on admission revealed 75 per cent (12 Gm) hemoglobin, 4,700,000 red cells and 15,040 white cells, consisting of 90 per cent polymorphonuclear cells, 8 per cent lymphocytes and 2 per

cent monocytes. The hematocrit reading was 46 per cent. The sedimentation rate was 35 mm per hour (Wintrobe, corrected). Urinalysis gave essentially normal results on several occasions. Additional studies of the blood revealed 91 mg of urea per hundred cubic centimeters, dextrose (fasting) varying from 108 to 93 mg per hundred cubic centimeters, a carbon dioxide-combining power of 44 volumes per cent, alkaline phosphatase 4.4 Bodansky units and phosphorus 4.2 mg per hundred cubic centimeters. Kline and Kolmer tests gave negative results. Culture of blood and agglutination tests for typhoid, undulant fever, typhus and tularemia also gave negative results. Examinations of the sputum for acid-fast bacilli, fungi and other organisms repeatedly failed to reveal any, except for the presence of *Monilia* on one occasion. The reaction to the Mantoux test was negative with a concentration of 1:100 of old tuberculin.

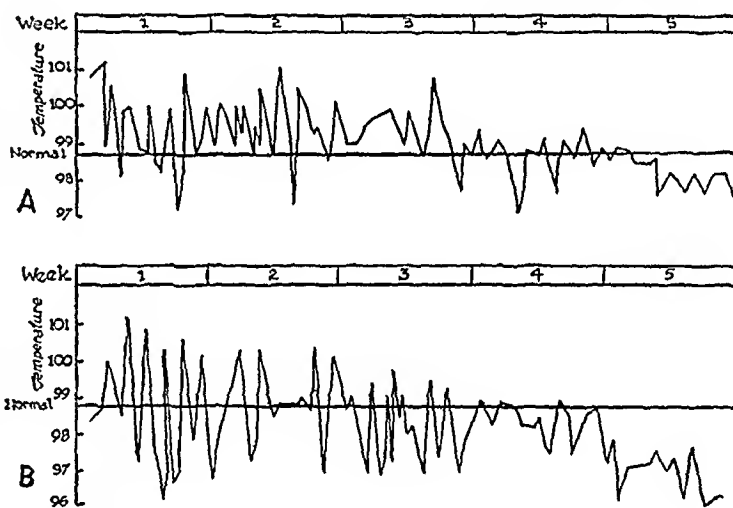


Fig 1—Temperature charts of patients 1 (chart A) and 2 (chart B), showing the febrile course of the disease during the stay in the hospital.

The Frei test and brucellergen cutaneous tests gave negative results.

Roentgen examination of the chest on the patient's admission revealed diffuse, fine infiltration throughout both lungs. The course of this infiltration is shown in serial roentgenograms reproduced in figure 2.

During observation in the hospital the patient manifested for three weeks an intermittent fever, reaching its peak late in the afternoon (fig 1A). The pulse rate was constantly elevated above 100 per minute, often attaining 115. The respiratory rate remained elevated, once reaching 80 per minute. On the day after admission, the patient had hemoptysis of small amount, which subsided quickly.

Therapy in the initial weeks was chiefly supportive, with a high caloric diet. On October 27 administration of potassium iodide, in doses totaling 37 grams (2.4 Gm)

From the Departments of Preventive Medicine and Medicine, School of Medicine, Tulane University of Louisiana, and Charity Hospital of Louisiana at New Orleans.

1 (a) Jamison, C, and Hopkins, J. Bagassosis. A. Fungus Disease of the Lung, New Orleans M & S J 93:580-582 (May) 1941. (b) Castleden, L I M, and Hamilton-Paterson, J L. Bagassosis. An Industrial Lung Disease, Brit M J 2:478-480 (Oct 24) 1942. (c) Gillison, J A, and Taylor, F. Four Cases of Bagassosis, ibid 2:577-578 (Nov 14) 1942.

daily, was begun, and this was continued until the patient was discharged. After the institution of this therapy the temperature curve remained within normal limits, the pulse rate gradually slowed to an average level of 80 per minute and the respirations within two weeks slowed to an average of 25 per minute. Subjectively and objectively the patient was greatly improved. Dyspnea disappeared. Physical examination continued to reveal a paucity of abnormalities. No rales were heard at any time, and bronchovesicular and suppressed breath sounds of slight degree were heard in the lower left quadrant of the chest posteriorly.

On November 17 the patient's blood showed a red cell count of 6,000,000, 85 per cent hemoglobin (Sahli) and a white cell count of 13,560, with 73 per cent poly-

On the day of discharge, the patient had a normal electrocardiogram, and fluoroscopic examination of the heart and great vessels showed them to be normal. The vital capacity was repeatedly 1,700 cc, a deviation of 60 per cent minus (Wilson) from the normal for the age, height and weight of the patient. The roentgenologic examination showed little change in the lesions in the chest. The physical examination revealed no abnormalities, and there were no subjective complaints. The hematocrit reading at the time was 42 and the red blood cell count 6,190,000. The hemoglobin content was 112 per cent, or 16.3 Gm per hundred cubic centimeters.

A follow-up examination on Dec 21, 1942, approximately one month after the patient's discharge, showed a gain in weight to 121 pounds (54.5 Kg). There was

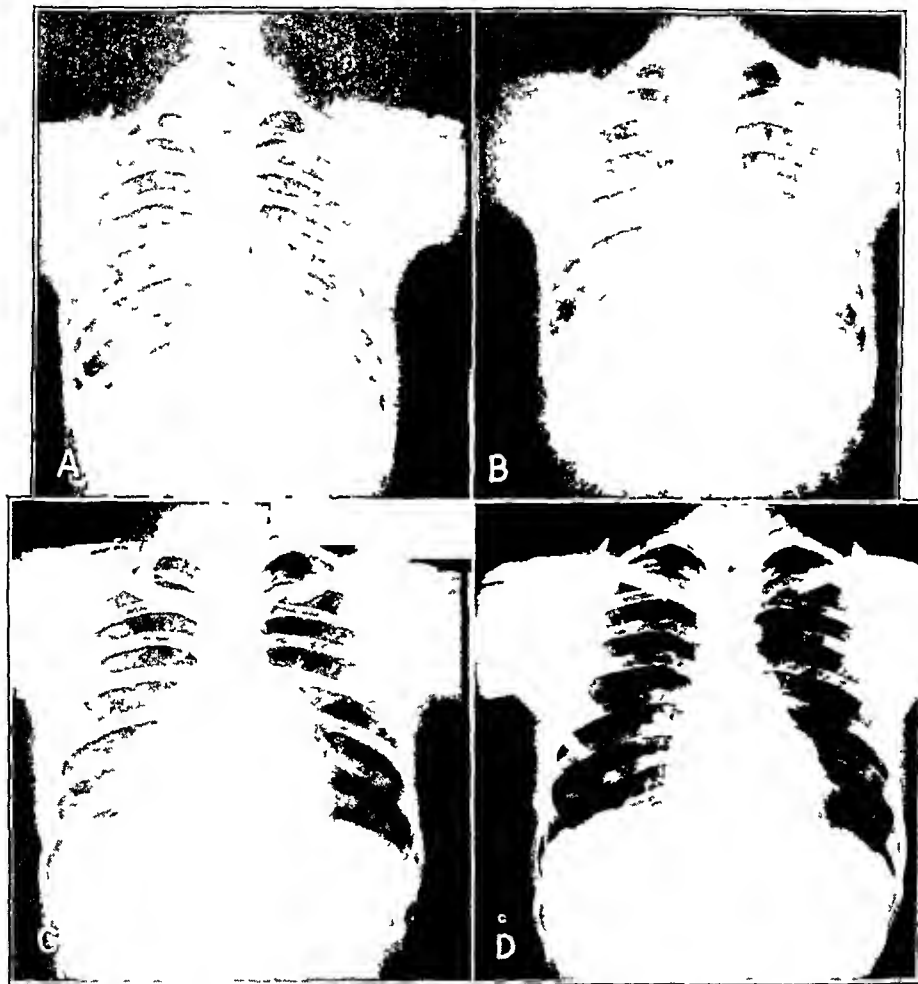


Fig 2—Roentgenograms of the chest of patient 1, taken (A) on admission, (B) the following day, (C) five weeks and (D) eleven weeks later. The last plate (D) shows complete resolution.

morphonuclear cells, 16 per cent lymphocytes, 7 per cent monocytes and 4 per cent eosinophils, the sedimentation rate was 54 mm per hour (Wintrobe, corrected). The hematocrit reading was 48 per cent. A week later the sedimentation rate was 65 mm per hour (Wintrobe, corrected) and the red cell count was 6,100,000.

The patient stated that he had weighed 140 pounds (63 Kg) prior to beginning work with bagasse. At the time of admission to the hospital he weighed 114 pounds (51.3 Kg), a loss of 26 pounds (11.7 Kg), according to the history, within one month, and during the ensuing three and a half weeks before iodide therapy was started he continued to lose steadily, his weight dropping to 109 pounds (49 Kg). With the administration of iodides gain in weight began, and it continued steadily until, at the time of discharge, on November 25, the patient weighed 117½ pounds (52.9 Kg).

slight dyspnea on mild exertion but none at rest. Cough was infrequent, with a small amount, less than a teaspoon, of yellow sputum expectorated in the morning. The lungs appeared clear on physical examination but not in roentgenograms, although some clearing was reported (fig 2). The temperature was 99.4 F, and the pulse and the respiratory rate were 80 and 21 per minute, respectively. The vital capacity had increased to 2,050 cc. The sedimentation rate and the white cell count of the blood were normal, but the hemoglobin content was still high, 140 per cent. Later a roentgenogram (fig 2) showed complete clearing.

CASE 2—F T, a 46 year old white man, married, entered the hospital on Sept 23, 1942, complaining of tightness in the chest, dyspnea and a sense of smothering. The onset had been gradual, and these symptoms had

continued to grow worse. Two weeks prior to admission, the patient began to have chills at night followed by severe drenching sweats which saturated the bedclothes. He believed that fever was present but was unable to measure it. These symptoms continued until a week prior to his admission to the hospital. Dyspnea on exertion was severe, forcing him to lie down to rest. A mild, unproductive cough had been present since the onset. No hemoptysis or foul-smelling sputum was noted. In seven months the patient lost 10 pounds (4.5 Kg).

The patient stated that he had been a farmer all his life. Three weeks prior to admission he began to work in an industrial plant breaking bagasse with a pick-

axe, 2 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 14 mm per minute (Rourke-Ernstene) and 40 mm per hour (Wintrobe, corrected). The hematocrit reading was 48.5 per cent, and the white cell count a week later was 13,350, with 102 per cent hemoglobin (149 Gm) per hundred cubic centimeters. Urinalysis repeatedly gave results within normal limits. The reactions to Kline and Kolmer tests were negative. Additional studies of the blood revealed 111 and 129 mg of urea per hundred cubic centimeters, 95 and 91 mg of dextrose per hundred cubic centimeters (fasting values) and a carbon dioxide-combining power of 40 volumes per cent on admission and 50 volumes per cent three weeks later. The calcium

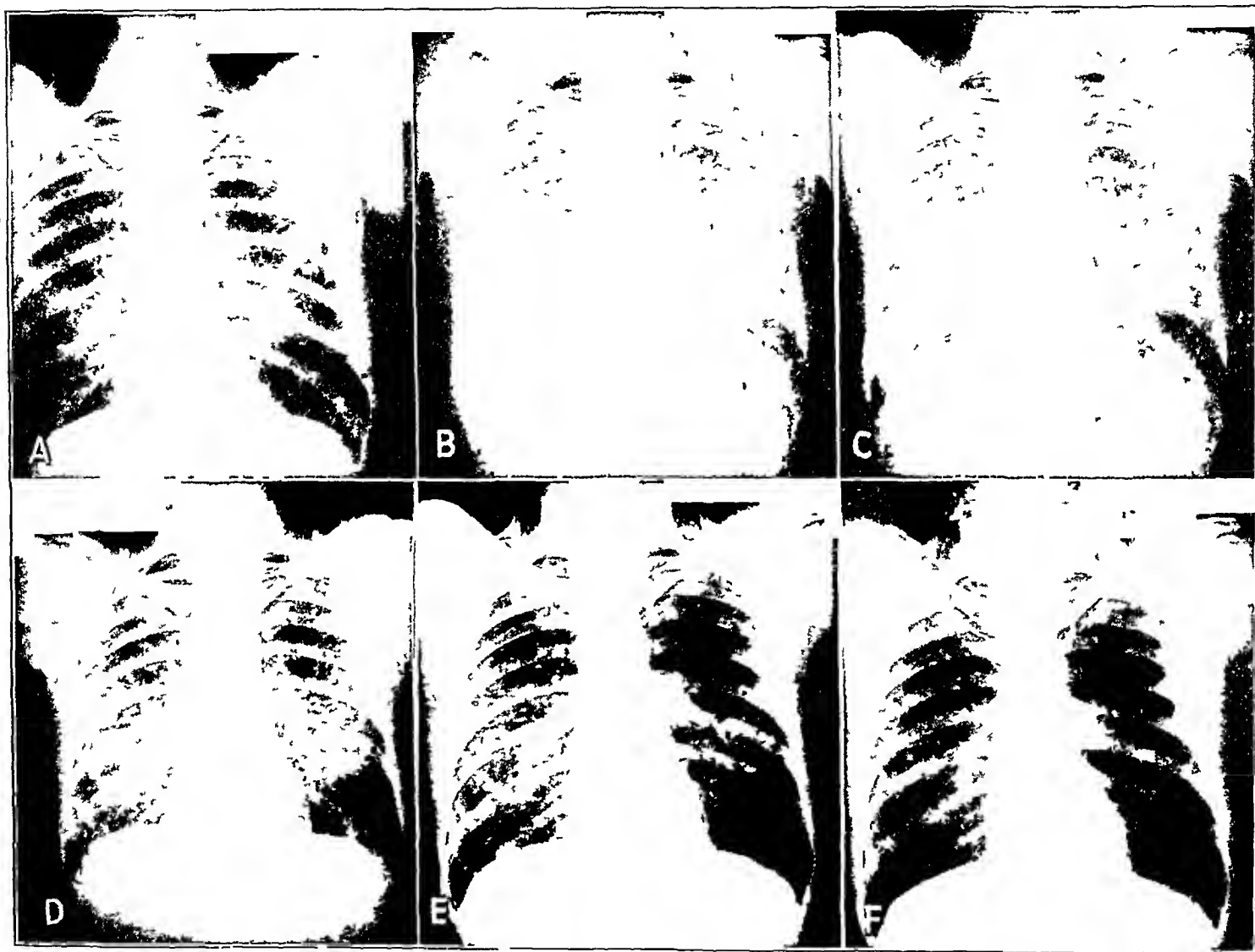


Fig 3—Roentgenograms of the chest of patient 2, taken (A) on admission, (B) two weeks later and (C) to (F) over the succeeding four month period. Note the increasing infiltration from (A) to (B) and the gradual but not complete resolution from (C) to (F).

He stated that there was not much dust and that he did not wear a mask but did keep a rag over his nose and mouth all the time he was working.

At the time of admission the patient did not appear acutely ill. The temperature was 98.2 F, the pulse rate 100 per minute, the respiratory rate 22 per minute and the blood pressure 108 systolic and 76 diastolic. No generalized lymphadenopathy could be demonstrated. The physical examination revealed no abnormalities on admission.

A blood count at the time the patient entered the hospital revealed 4,600,000 red blood cells, 70 per cent hemoglobin (112 Gm), 7,400 white blood cells, 80 per cent polymorphonuclear cells, 15 per cent lympho-

cytes, 2 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 14 mm per minute (Rourke-Ernstene) and 40 mm per hour (Wintrobe, corrected). The hematocrit reading was 48.5 per cent, and the white cell count a week later was 13,350, with 102 per cent hemoglobin (149 Gm) per hundred cubic centimeters. The phosphorus content, 41 mg. The value for alkaline phosphatase was 17 Bodansky units. The result of the Frei test was negative. The Mantoux test elicited a 2 plus reaction with a concentration of old tuberculin of 1:10,000. Culture of the blood gave negative results, as did agglutination tests of the blood for typhoid, typhus, undulant fever and tularemia. Studies of the sputum for acid-fast bacilli and for fungi repeatedly failed to reveal any. The result of the brucellergen test was negative.

The roentgenologic report on the patient's admission showed diffuse mottled infiltration throughout both pulmonary fields. Serial roentgenograms taken during his stay in the hospital are shown in figure 3.

On the day of admission the patient weighed 115 pounds (51.75 Kg), and during the ensuing four weeks the weight varied from 113 to 117 pounds (50.9 to 52.7 Kg). For the first two weeks in the hospital the patient manifested an irregular, intermittent fever, the temperature reaching 101.2 F, which gradually receded so that the temperature returned to normal by the end of the third week (fig 1B). The pulse rate for the first four weeks of hospitalization averaged 100 per minute, but it fluctuated considerably, once attaining 120 per minute. During the febrile episodes the respirations averaged 30 to 40 per minute, once reaching a level of 45.

At the end of the fifth week of hospitalization, potassium iodide therapy was begun, with a total dose of 37 grains (2.35 Gm) a day. Thereafter, no further febrile episodes were noted. The pulse and the respirations improved gradually until at the end of the fourth week of therapy the pulse rate averaged 95 per minute and the respiratory rate fluctuated between 20 and 30 per minute. Gain in weight was slow and steady until on the day of discharge, the patient weighed 122 pounds (54.9 Kg). Throughout his stay in the hospital the subjective complaints gradually and steadily improved, although rales of fine, crackling character developed in the base of the right lung posteriorly and persisted until the day of discharge.

On the day of discharge the patient's vital capacity was 1,555 cc, which is minus 60 per cent deviation from normal for the age, weight and height (Wilson). Fluoroscopic examination of the heart and the great vessels revealed no abnormalities. The electrocardiogram was within normal limits. The roentgenogram showed relatively little improvement.

On Dec 21, 1942, approximately a month after discharge, the weight was 126½ pounds (56.9 Kg). Shortness of breath occurred on mild exertion, and there was some morning cough. Fine rales were numerous over both bases posteriorly. Vital capacity had risen to 2,000 cc. The hemoglobin was 123 per cent (17.8 Gm) and the sedimentation rate and white cell count 18 mm and 4,850 respectively. A roentgenogram of the chest taken in the eleventh week of the disease showed considerable, but not complete, clearing (fig 3).

#### COMMENT

The table summarizes the outstanding clinical findings in these 2 as well as in the 9 remaining cases. Clearly the factors of sex and age are likely to depend on selection of workers in bagasse on the basis of ability to perform manual labor. Hence, all the patients were men, and their ages averaged 27 years. Six were white, and 5 were Negro. The length of exposure to bagasse dust before symptoms arose was known in 8 cases and varied from three weeks to two years. A clearcut history of exposure for only three weeks to two months was obtained in 3 of these cases. In Gillison and Taylor's cases this period was from two to four months.<sup>1c</sup>

The symptomatic picture was variable but showed several rather constant characterizing features. Cough and dyspnea were early and important symptoms. Dyspnea occurred in all and was almost invariably the presenting complaint. Characteristically it appeared suddenly

and became sufficiently severe within a few days to force the patient to rest. Cyanosis was noted but once. Cough occurred in all instances. Hemoptysis was noted 4 times, it was of short duration (several days) and the amount of blood varied, not exceeding a teaspoon daily. In general the sputum, which was raised in 9 instances, was scant and mucoid. It had a whitish appearance except when blood tinged. Others<sup>1c</sup> have described the sputum as dark and yellow, dirty and foul smelling. None of our patients described the sputum in these terms. Pharyngeal irritation was noted in 3 instances. Pleural pain was not observed but retrosternal pain was associated with dyspnea and cough. Night sweats, chills and fever were not infrequent. In one of our most recent patients, as well as in the one reported by Jamison and Hopkins, malaria was suspected and a diligent search made to rule it out. The fever charts of patients 1 and 2 are shown in figure 1. Intermittent fever, with temperature ranging from 99.8 to 101.2 F, was observed and persisted up to three or four weeks. In 3 patients no fever was noted. Tachycardia with a heart rate exceeding 100 per minute occurred in 4 patients. The respiratory rate varied from 20 to 80 and was over 25 in 7 patients during the episodes of fever and dyspnea. For 8 of the 11 patients the weight was recorded. In all of them loss of weight occurred, varying from 5 pounds (2.25 Kg) in three weeks to 26 pounds (11.7 Kg) in two months. It was frequently noted before other symptoms developed. Weakness over a long period was a characteristic finding. The blood pressure was not remarkably changed.

Examination of the chest revealed nothing striking. Impaired resonance and diminished breath sounds were noted in 4 instances, usually in the bases of the lungs posteriorly. In 8 patients rales were heard, chiefly in the bases. In 1 instance minimal signs of consolidation were heard in the base of the right lung, an area in which lung puncture with biopsy was successful. The manifestations were bilateral in 6 instances.

Roentgen examination of the chest showed what was uniformly described as a milary mottling throughout both lungs, most dense in the hilar areas. These areas in general had a ground glass appearance. In only 1 instance were the apexes involved. Examples of these changes and of their progress are presented in figures 2 and 3.

Bronchoscopy was carried out for 1 patient, and nothing worthy of note was observed. Bronchograms also failed to reveal anything significant. In Gillison and Taylor's patients bronchoscopy showed congestion of the trachea

# Summary of Clinical Data on Cases Reported

Case No	Age	Race	Length of Exposure (Weeks)	Cough	Dyspnea	Sputum	Hemoptysis	Night Sweats	Chills and Fever	Loss of Weight (Pounds)	Pharyngeal Irritation	Duration of Symptoms Before Admission (Weeks)	Cyanosis	Examination of Chest	Roentgenologic Picture of Chest	Days of Hospitalization	Follow Up
1	18	W	4	+	+	+	+	0	0	26	0	1	0	Diminished breath and voice sounds over base of left lung, with limited expansion, no rales	Miliary ground glass mottling throughout both pulmonary fields, radiating from hili, apexes clear (fig 2)	84	Chest roentgeno logically clear (fig 2) 1 month after discharge
2	46	W	3	+	+	+	0	+	+	10	0	1	0	Rales in bases of both lungs anteriorly and posteriorly	As above (fig 3)	93	Chest roentgeno logically clear 11 weeks after discharge
3	26	W	20	+	+	0	0	+	+	17	0	4	0	Impaired resonance and breath sounds in base of right lung, bilateral basal rales	As above	23	
4	30	N	6	+	+	+	0	—	—		+	3	0	Impaired resonance and diminished breath sounds in bases of both lungs posteriorly	As above	31	Chest roentgeno logically clear 13 weeks after discharge
5	34	N		+	+	+	0	—	+	15	0	5	0	Impaired resonance upper lobe of right lung anteriorly, no rales	As above	9	Chest roentgeno logically clear 13 weeks after discharge
6	10	W	28	+	+	+	0	—	—	20	0	12	0	Fine crackling rales at base of left lung posteriorly only	As above	19	Chest roentgeno logically slightly cleared on discharge, no follow up
7	27	N	104	+	+	0	0	+	+	5	+	3	0	Fine rales in base of right lung posteriorly and in right axilla	As above	18	No follow up
8	28	N	12	+	+	+	+	+	+		—	3	0	Rales in upper half of right side of chest, vocal fremitus increased	Apexes also involved	15	No follow up
9	27	W		+	+	+	+	+	+	amt ?	—	5	+	Diminished expansion at bases of both lungs, rales throughout both lungs, most marked in bases	Miliary ground glass mottling throughout both pulmonary fields, radiating from hili apexes clear	86	Chest roentgeno logically clear 2½ months after discharge
10	22	W		+	+	+	0	+	+	amt ?	—	3	0	Fine rales bilaterally throughout pulmonary fields	As above	14	No follow up
11	20	N	16	+	+	+	+	+	+		+	2	—	Diminished expansion at bases of both lungs, coarse rales at base of right lung posteriorly	As above	29	Chest roentgeno logically clear 1 month after discharge

and bronchi and a white frothy sputum. These were noted in the late stages of the disease.

The sputum, already described as scanty and mucoid, persistently failed to reveal tubercle bacilli, even with concentration methods. In 4 cases repeated attempts were made to grow a fungus. On 1 occasion a positive culture for *Monilia* was obtained, in another patient a fungus was found but not identified. These organisms were considered as contaminants. The cellular content of the sputum consisted, in general, of polymorphonuclear leukocytes and lymphocytes. Eosinophils were not in evidence.

Studies of the blood were of interest. Leukocyte counts varied from 7,400 to 20,600. Ten of the 11 patients had counts above 10,000, averaging approximately 13,000. In 7 cases differential counts indicated polymorphonuclear leukocytosis, the percentage of polymorphonuclear cells varying from 73 to 90. Toxic granulations were in evidence, and there was a shift to the left. The proportion of eosinophils varied from 0.5 to 7 per cent, averaging 3.5 per cent. The numbers of mononuclears and of lymphocytes were in the normal range. In 5 cases Wintrobe sedimentation rates were 35 to 54 mm per hour, a definite increase. In 4 instances the hematocrit reading was 46, and in 1 it was 48.5. The red blood cell counts on admission varied from 4,300,000 to 6,770,000 in 9 cases. The high value, of 6,770,000, occurred in the fifth week of the disease and was accompanied by a febrile reaction of 101 F. In cases 1 and 2 we noted the development of a polycythemia in the eighth and the twentieth week of the disease, respectively. This finding has not been recorded previously perhaps because of the lack of follow-up studies. The hemoglobin values were correspondingly elevated. Blood cultures and agglutination reactions for typhoid, paratyphoid, tularemia and undulant fever were negative in 3 cases. In cases 1 and 2 tests for psittacosis, carried out by Dr. Karl Meyer, of the Hooper Foundation, gave negative results. Routine urinalyses and determinations of blood chemistry were within normal variations.

A Mantoux test was done in 4 cases. In 2, the reaction was negative with dilutions of old tuberculin of 1:1,000 and 1:100. Cutaneous tests with bagasse extracts will be described later in the paper.

Treatment has consisted of rest in bed during the acute stages of the disease and palliative medication and procedures. In the 2 cases reported in detail a relationship between improvement and the administration of potassium iodide seemed to be evident. This change may have been coincidental.

The stay in the hospital varied from nine to ninety-three days and averaged thirty-eight and a third days. A follow-up investigation of 6 cases over periods of four months showed perfectly clear roentgenograms of the chest in 5 and a residual which appears at present to be clearing in 1.

Jamison and Hopkins called the condition "bagasscosis", according to Castleden and Hamilton-Paterson the term "bagassosis" is better. Since the suffix "osis" is properly added only to words formed from Greek roots<sup>2</sup> and since we have as yet not been able to trace the term "bagasse" to the Greek, we prefer the simple term "bagasse disease of the lungs."

The cause of the clinical picture has been undetermined. The lack of autopsy material has handicapped the search for the cause. We have been fortunate in obtaining sections of a lung of 1 patient at autopsy and of another by lung puncture.<sup>3</sup> The observations on these sections will be discussed. Experimental production of the disease has thus far failed. A relationship between the development of the picture and work in bagasse dust seems clear. This association was noted by Jamison and Hopkins<sup>1a</sup> as well as by others<sup>1b, c</sup>. Although bagasse dust up to the present time has not been shown conclusively to be the cause of the symptoms, the close relationship between the patients' work and the characteristic clinical picture, together with the absence of the disease in other persons, so far as observers have noted, points clearly to a cause and effect relationship between exposure to bagasse dust and the development of symptoms. As will be discussed later, we have identified bagasse dust in sections of lungs.

In their report Jamison and Hopkins suggested a fungus as the cause. They isolated a fungus but did not state its characteristics or type. In one instance we found *Monilia* in the sputum but considered that it was probably a contaminant, as is often the case. Castleden and Hamilton-Paterson attempted without success to isolate a fungus. Gillison and Taylor had the same experience. The roentgenograms of the chest remind one somewhat of the maple bark disease,<sup>4</sup> a fungus infection, but we have been unable to

2 Garber, S. T. *Stedman's Practical Medical Dictionary*, ed 15, Baltimore, Williams & Wilkins Company, 1942.

3 Sodeman, W. A., and Pullen, R. L. Bagasse Disease of the Lungs, *New Orleans M. & S. J.* 95: 558-560 (June) 1943.

4 Towey, J. W., Sweany, H. C., and Huron, W. H. Severe Bronchial Asthma Apparently Due to Fungus Spores Found in Maple Bark, *J. A. M. A.* 99: 453-459 (Aug. 6) 1932.



isolate the causative organism or any other organism which would produce a similar picture. Investigation of the bagasse itself is difficult. After lying in the field for variable lengths of time with fermentation and fungous and bacterial invasion taking place in the bales, bagasse is a complex mixture not easy to analyze. One might mention, however, that workers exposed to dust of the insulation board after processing, which includes heat treatment, have not as yet been reported to acquire bagasse disease. Processing destroys not only fungi and bacteria but allergenic protein as well. The fungus theory has at present little supporting evidence, but an infectious theory cannot be disproved on negative or indirect grounds.

Some relationship to byssinosis, the syndrome occurring among persons working with low grade stained cotton, might be suspected. This syndrome is an acute illness that develops in workers exposed to high concentrations of dust, particularly in rural mattress making centers, cotton mills and upholstering plants,<sup>5</sup> and is thought to be caused by inhalation of substances produced by certain gram-negative bacteria in or on the dust. However, the clinical picture is distinctly different from that of bagasse disease. The onset is sudden, within a few hours after exposure. Dry throat, aches, fatigue, headache, cough, chills, fever, and nausea and vomiting occur. Conjunctival irritation is present. The symptoms in the acute phase last only one to two days.

Castleden and Hamilton-Paterson<sup>1b</sup> suggested an allergic reaction as the cause of bagasse disease. They based this suggestion on the positive results of cutaneous tests. Realizing the possibility that an allergic factor could be responsible for the disease, they prepared extracts for the tests in four menstruums: tenth-normal solution of sodium hydroxide, tenth-normal hydrochloric acid, isotonic solution of sodium chloride and 30 per cent alcohol in distilled water. Tricresol, 0.25 per cent, was added to each. The extracts containing acid and alkali were neutralized before use. In their case 2, extracts 1, 2 and 4, given intracutaneously in doses of 0.2 cc, all elicited a wheal maximal in thirty minutes and a flare maximal in thirty-six hours. Controls of the menstruum were also prepared. The saline extract gave a flare but no wheal. Three patients tested gave positive reactions, and a group of controls who did not have bagasse disease was

reported as having negative reactions. It appears that these were tested solely with the saline extract, the one which in their case 2 caused a flare only, without a wheal.

From these results Castleden and Hamilton-Paterson concluded that whole bagasse contains an antigen soluble in isotonic solution of sodium chloride to which workers inhaling the dust can be sensitized. They suggested that the acute phase of the disease is possibly an allergic response to this antigen, with, or probably without, an infective element.

We repeated these tests on our patients. Through the efforts of Dr S. S. Pinto, chief of the section of industrial hygiene of the Louisiana State Department of Health, we were able to obtain a sample of bagasse from a bale bound for England. Dr Vincent Derbes, allergist to the Hutchinson Memorial Clinic, made up extracts of this material according to the directions of Castleden and Hamilton-Paterson. With all four extracts we tested 3 patients, 2 after recovery from the disease and 1 during the sixth week of the disease. In addition, 5 controls, 3 who had no knowledge of ever contacting bagasse, 1 who in his youth had cut cane for several weeks and another who had worked as watchman in an area where bales of bagasse were stored, were tested. The doses of the English observers, as well as 0.04 cc doses, were used intracutaneously. The developing reactions in 5 of these subjects were traced at the end of thirty minutes, with the results shown in figure 4. Positive results were obtained in each instance, which led us to the conclusion that the reactions were irritation phenomena, perhaps with release of histamine, and did not necessarily indicate sensitization to bagasse. At each site, particularly with the sodium hydroxide and the saline extract, extensive areas of reaction twice or more the size of the immediate flare were seen at twenty-four to thirty-six hours. This reaction was not the flare of Lewis' triple response but a diffuse redness of the type seen in the positive reactions to the tuberculin test and similar tests. Of its interpretation we are in doubt, but, as is well known, the response cannot be construed to indicate an allergy to the extract used. We encountered no absolutely negative reactions to tests, as did Castleden and Hamilton-Paterson. Dr Derbes concurred in these interpretations. Allergic pulmonary disease is well known. The syndrome described by Loeffler appears to be such. It is a transient pulmonary infiltration accompanied by eosinophilia in the blood, and, as in the present series of patients, eventuates in the spontaneous disappearance of symptoms.

5. Schnitzer, R., Neal, P. A., and Caminita, B. H. Etiology of Acute Illness Among Workers Using Low-Grade Stained Cotton, *Am J Pub Health* 32: 1345-1359 (Dec.) 1942.

and signs<sup>6</sup> The course of the disease is, however, distinctly different Symptoms include attacks of asthma with cough, fever, leukocytosis, eosinophilia and elevated sedimentation rate Only a few rales are heard over the involved pulmonary areas Roentgen findings differ considerably, with areas of consolidation appearing and disappearing rapidly, and the picture clears up in about a week, with only a few fine scars left in the lung

Tuberculosis is to be suspected as the cause of the condition, especially from the roentgen appearance of the lungs The clinical associations, the absence of tubercle bacilli in the sputum when it is examined by concentration methods, the results of the tuberculin test and the course of the disease, together with observations made at

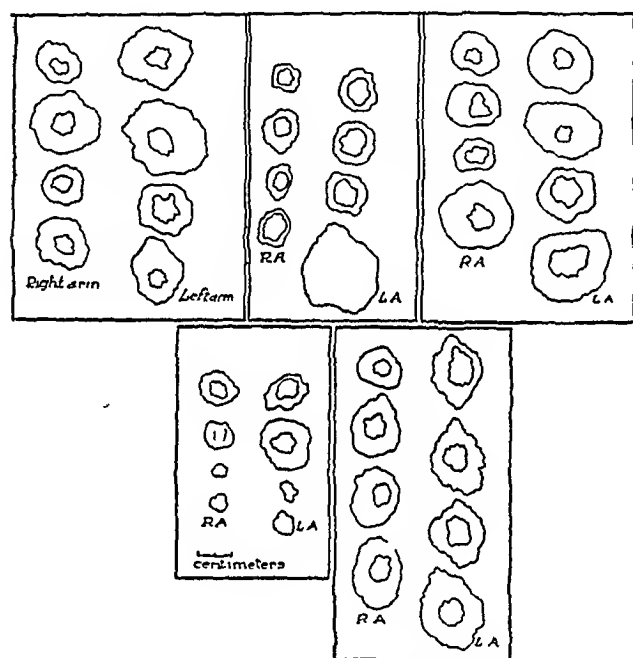


Fig 4—Tracings taken at the end of thirty minutes of the cutaneous responses to intracutaneous injection of extracts of bagasse in 5 subjects The central area in each instance represents the wheal and the large area the extent of the flare In each arm the reactions from above downward represent the response to bagasse extracted in (1) 30 per cent alcohol, (2) tenth-normal sodium hydroxide solution, (3) tenth-normal hydrochloric acid, and (4) isotonic solution of sodium chloride (see text) Reactions in the right arm in each instance represent the response to 0.04 cc of extract, in the left arm, to 0.2 cc The responses shown in the last diagram were found in the sixth week of the disease (case 3) The remaining responses are from the control series

biopsy and at autopsy, rule it out rather conclusively On similar grounds Boeck's sarcoid is eliminated

Finally to be considered as a possible cause of the clinical picture is pneumoconiosis This

general term covers all diseases due to dust, whether fibrous or nonfibrous<sup>7</sup> While bagasse is described as containing 5 to 7 per cent silica (silicon dioxide), the short incubation period of the disease and its short course, with complete clearing of the lungs from the clinical and roentgenologic standpoints, speak distinctly against the possibility that the picture is a phase or type of silicosis, even of the acute variety Castleden and Paterson's patient with residual lesions had worked as a coal miner for twenty years<sup>1b</sup>

Exposure to a variety of organic and inorganic dusts other than those active from their silica content may produce symptoms Bronchitis is not uncommon, and its cause often goes unrecognized Particles sufficiently small may reach the alveoli and set up a pneumonitis Our patients showed roentgen evidence, leukocytosis, variable degrees of fever and raising of sputum, all of which are compatible with a diagnosis of pneumonitis The usual types of pneumonia, including atypical or virus pneumonia, are so different in all respects from this syndrome that they seem out of the picture But a pneumonitis from dust is likely, and the examination of tissue obtained by lung puncture from a patient in the sixth and seventh weeks of the disease supports the view that bagasse particles mechanically, chemically, through one of its fractions or by introduction of an unknown infection, are responsible for the pathologic picture Sections of these specimens obtained from involved areas are reproduced in figure 5 A section from the first biopsy specimen and one obtained at an autopsy in a case of bagasse disease have previously been published<sup>3</sup> In that report the first biopsy was described as showing pulmonary tissue with several "spicules" of an irregular foreign material embedded in it The foreign bodies were similar microscopically to bagasse Under the polarizing microscope these "spicules" were seen to rotate polarized light This examination brought out many smaller scattered pieces, with an average diameter of 2 to 8 microns These structures were seen especially in the fibroblastic reaction of the interstitial tissue of the lung Dr B Pearson of the department of pathology, who reviewed all these sections, described the second biopsy specimen, taken a week later, as follows

The specimen showed a reaction similar to the first, but there were only a few "spicules" and these were of the smaller variety previously described They were present in areas in which there was an increase in fibrous tissue and reacted as bagasse fibers characteristically do to polarized light An additional feature

<sup>6</sup> Hoff, A, and Hicks, H M Transient Pulmonary Infiltrations, *Am Rev Tuberc* 45 194-199 (Feb) 1942

<sup>7</sup> Harrington, D, and Davenport, S J Review of Literature on Effects of Breathing Dusts with Special Reference to Silicosis, Bulletin 400, United States Department of the Interior, Bureau of Mines, 1937

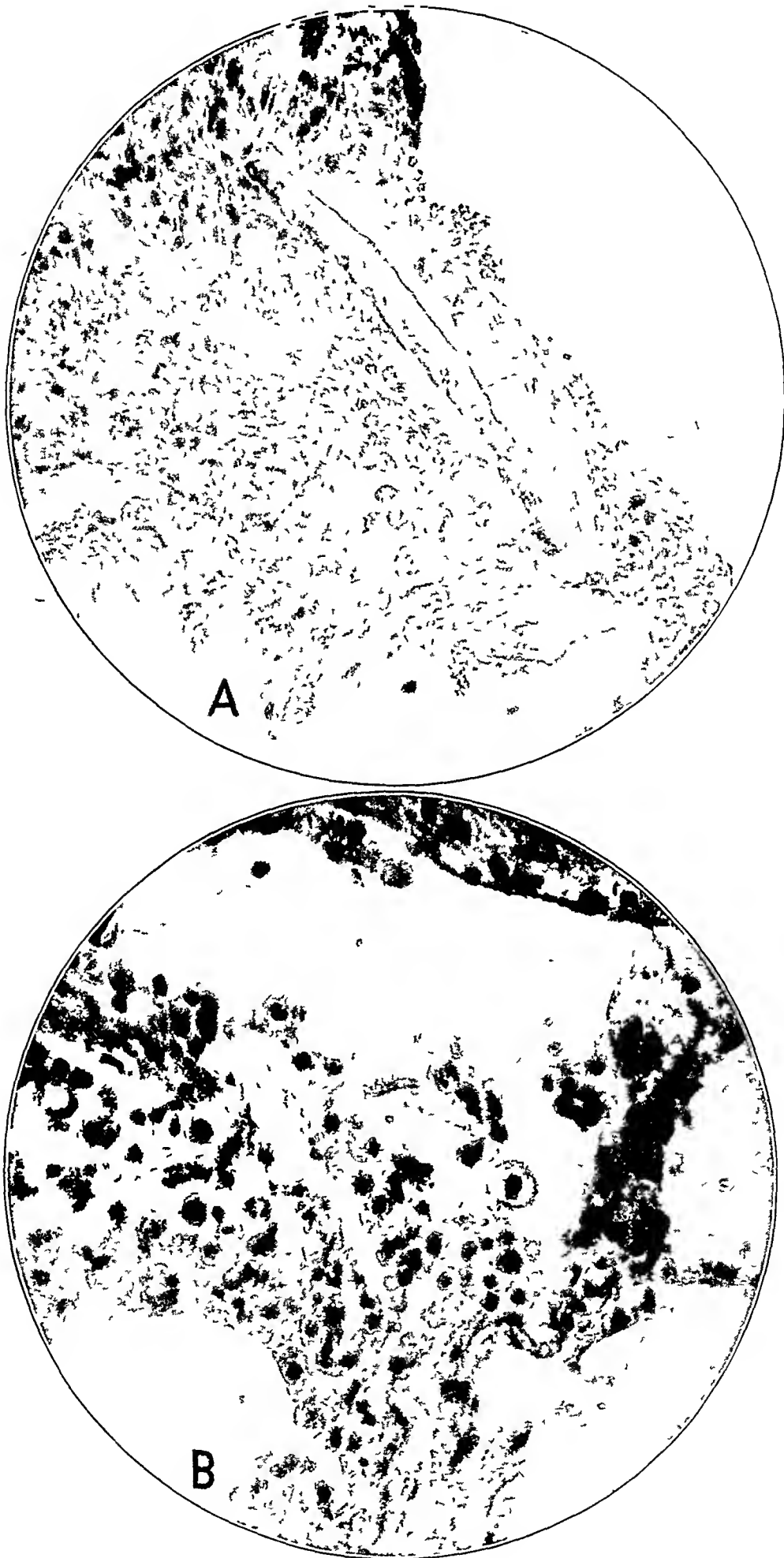


Fig 5—Sections of needle biopsy specimens of the lung obtained from patient 3 in the sixth (A) and seventh (B) weeks of the disease

was the many large cells with a foamy cytoplasm in the alveolar spaces

The section of lung obtained at autopsy<sup>3</sup> also showed a fibroblastic reaction of the interstitial tissue. Spicules were not as numerous, but the alveolar cells with foamy cytoplasm were larger and more numerous, in some areas filling the alveolar spaces.

It appears that particles of bagasse may enter the alveolar regions and initiate the reaction described and that by digestion or absorption through the activity of the cellular response they may be removed and a normally functioning lung, clear on roentgen examination, remain. The mechanism of the changes and the nature of the stimulus set up by the bagasse dust to produce the cellular reaction are obscure. These

are the first demonstrations we have seen of this reaction in the tissues of a patient with bagasse disease. The clinical picture, from the striking dyspnea to the later polycythemia, may be explained as due to the effects of this reaction and the anoxia resultant therefrom.

#### SUMMARY

Eleven cases of bagasse disease of the lung have been added to the literature, bringing the total number of reported cases to 18. Observations of the group disclose a number of constant features which produce a characteristic clinical picture. Evidence from histologic study of involved areas of the lung indicates the presence of bagasse dust with a severe and unusual cellular reaction, the nature of which has not yet been established.

# DIFFUSE ISOLATED MYOCARDITIS ASSOCIATED WITH DIETARY DEFICIENCY

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In recent years there have appeared in the literature many reports describing unusual cases of myocarditis of unknown cause. Various appellations have been applied to the myocardial disease: Fiedler's myocarditis, diffuse isolated myocarditis, myocarditis perniciosa, diffuse granulomatous myocarditis and others. The condition is usually attributed to such causes as infections of the upper respiratory tract, influenza, burns, toxemias and injuries produced by various chemicals. Magner<sup>1</sup> expressed the opinion that obscurity of cause could not be considered as justification for the grouping together of these conditions as manifestations of a single disease. It appeared to him that the group is a heterogeneous one, possibly including atypical varieties of tuberculous, syphilitic and rheumatic myocarditis as well as certain other inflammatory conditions of unknown and probably variable causation. However, Saphir,<sup>2</sup> who recently published an extensive review of the literature pertaining to myocarditis, stated the belief that "one is justified in accepting the occurrence of isolated myocarditis in the sense of a more or less diffuse inflammatory lesion if every known cause for this type of myocarditis is ruled out and if the myocarditis is found in the absence of any major pathologic condition involving either the endocardium and pericardium or the entire body." Lindberg<sup>3</sup> compared the myocardial lesions of his patient with the serous myocarditis described by Wenckebach<sup>4</sup> and others and suggested that isolated myocarditis might represent the end stage of beriberi. More recently, Smith and Furth<sup>5</sup> re-

ported 3 cases of fibrosis of the endocardium and myocardium with mural thrombosis. In these cases the changes were not attributable to arteriosclerosis, hypertension or valvular disease. There was abundant evidence of dietary deficiency, and the question was raised whether these changes could represent a variant of beriberi heart. The case presented here resembles pathologically those of Smith and Furth. The disease was associated with a prolonged history of malnutrition, and there is evidence indicating that dietary deficiency of vitamin B may have been an important etiologic factor. The case, therefore, seems worthy of record.

## REPORT OF A CASE

I. M., a 15 year old white girl, was admitted to the Royal Victoria Hospital, Montreal, on April 10, 1943, in a state of severe cardiac insufficiency. The family history was barren of relevant data. At birth the patient appeared normal in every way. In infancy she suffered from a "weeping eczema," which disappeared completely at the age of 3 years. At 5 she began to have a hacking productive cough which was severe in winter but mild in summer; thereafter, pharyngitis was frequently experienced, gain in weight was retarded and loss of color and of strength was progressive. At 7 she was admitted to the Montreal General Hospital, suffering from malnutrition and chronic tonsillitis. Heavy peribronchial shadows seen on roentgen examination suggested bronchiectasis, but this diagnosis was not further substantiated, and after two months of beneficial dietary and general supportive therapy she was discharged to a convalescent home in a much improved condition. In October 1942, at the age of 14 years, she was again admitted to the same hospital, complaining of cough. She was a poorly developed and malnourished girl who weighed approximately 35 pounds (15.9 Kg) less than average for her age and height. Roentgen examination of the chest revealed hilar and bronchovascular markings. An occasional extrasystole was detected, and the second heart sound was loud throughout the precordium, the blood pressure was 100 systolic and 60 diastolic. The electrocardiogram demonstrated an irregularity of sinus origin. In the first lead the QRS complex was notched in the upstroke. There were a slight delay in the conduction time and a suggestion of left axis deviation. An electrocardiogram made one week after the first showed the same delay in conduction. These findings were interpreted as evidence of an unstable cardiac conducting mechanism. The hemogram demonstrated a mild anemia of secondary type. During the seven week period of hospitalization there was no fever, and with rest in bed, high caloric diet, high vitamin intake and

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1 Magner, D. A Case of Fatal Subacute Myocarditis of Unknown Etiology, *Am J M Sc* **198** 246, 1939

2 Saphir, O. Myocarditis. A General Review, with an Analysis of Two Hundred and Forty Cases, *Arch Path* **32** 1000 (Dec) 1941, **33** 88 (Jan) 1942

3 Lindberg, K. Zur Frage von den sogenannten isolierten chronischen Myokarditen, *Acta med Scand* **95** 281, 1938

4 Wenckebach, K. F., cited by Saphir<sup>2</sup>

5 Smith, J. J., and Furth, J. Fibrosis of Endocardium and Myocardium with Mural Thrombosis, *Arch Int Med* **71**:602 (May) 1943

ultraviolet therapy improvement was striking. She had gained 12 pounds (5.4 Kg) (about a 20 per cent increase over the body weight on admission) when she was discharged, in December 1942.

The patient then returned home to continue as nearly as possible the hospital regimen which had been so beneficial. She resumed full activity and returned to school in January 1943. Her health remained fairly good until March, when she became increasingly restless, had frequent headaches, gradually lost weight and color and began to vomit occasionally. She experienced mild precordial pain and had dyspnea on slight exertion. Once or twice she coughed up bloody sputum, and on the day of readmission to the hospital she had a slight nosebleed.

On her final admission to the hospital, physical examination revealed no fever, the pulse rate was 108 and the respiratory rate 28 per minute. The patient was restless, dyspneic and pallid. There was pediculosis capitis. The pulse was soft, rapid and regular, and the blood pressure was 92 systolic and 70 diastolic. The heart was enlarged, the point of maximum impulse

low QRS voltage, split QRS complex and intraventricular time of sixteen-hundredths second. In lead I the T wave was diphasic, in lead IV there were high T voltage and elevation of the ST interval (fig 1).

The clinical diagnosis was congestive heart failure, but the nature of the underlying cause was not apparent. She was given digitalis, restricted fluids and a salt-free diet. Thiamine hydrochloride was injected intramuscularly in doses of 100 mg, and vitamins B and C were given by mouth. The rapid pulse and respiratory rates continued, and she remained afebrile. Occasionally she coughed blood-tinged sputum, and frequent use was made of the oxygen tent. On April 15 she became cyanotic, her breathing was labored and she complained of severe abdominal pain. Death occurred, somewhat unexpectedly, on April 16. An electrocardiogram made during the last minutes of life showed complete heart block (rate 15 per minute) and left bundle branch lesion terminating in ventricular fibrillation just before death.

*Postmortem Examination*—Autopsy two and one-half hours after death included examination of the thoracic and abdominal organs and the brain. The noteworthy conditions observed were the following.

*Gross Examination* The body, which measured 153 cm in length, was that of a poorly nourished girl showing early pubertal changes. The scleras and the skin were pale, and the lips and the oral mucosa were cyanotic. Greatly distended superficial veins were prominent in the neck. The rounded, moderately protuberant abdominal wall was covered by a thin layer of subcutaneous fat, and numerous striae had formed in the overlying skin. Pitting edema involved both lower extremities, the vulva and the sacral area. The tips of the fingers and toes were cyanotic but were not clubbed. Within the thorax, the heart and pericardial sac occupied the greater portion of the transverse diameter. The pericardial sac contained 75 cc of clear yellow fluid, the serous surfaces were free from lesions. The pulmonary artery, opened in situ, contained only an elongated mass of postmortem clot.

The heart (figs 2, 3 and 4) weighed 295 Gm. The pericardial membrane was everywhere thin and smooth. All the chambers were moderately dilated, and the pulmonary conus was distinctly larger than the aortic conus. Both ventricular walls were hypertrophied, the right measured 6 mm in thickness, and the left, 10 mm at the thickest portions. The myocardium had a variegated reddish brown to grayish brown mottled appearance, and its consistency was soft. However, several small irregular gray areas of firm consistency were noticeable on the cut edges of both ventricles. Near the endocardium the myocardium was much grayer and firmer than elsewhere. The trabeculae carneae and the papillary muscles were broad and flat, the pectinate muscles were unusually prominent. At a site a few centimeters from the aortic ring opposite the anterior margin of the interventricular septum the myocardium of the left ventricle showed a reddish brown area in the superficial half of its thickness. The circumferences of the valves were within normal limits, the leaflets and cusps appeared entirely normal. The mural endocardium of the right atrium was moderately thickened in a diffuse manner, and some small irregular gray patches of slight thickening were visible in the endocardium of the right ventricle overlying the interventricular septum. Greater and more extensive fibrous thickening was present diffusely throughout the endocardial lining of the left auricle and in wide areas of the mural endocardium of the left ventricle, especially over the interventricular septum and the anterior wall of the ventricle. Small gray firmly adherent mural

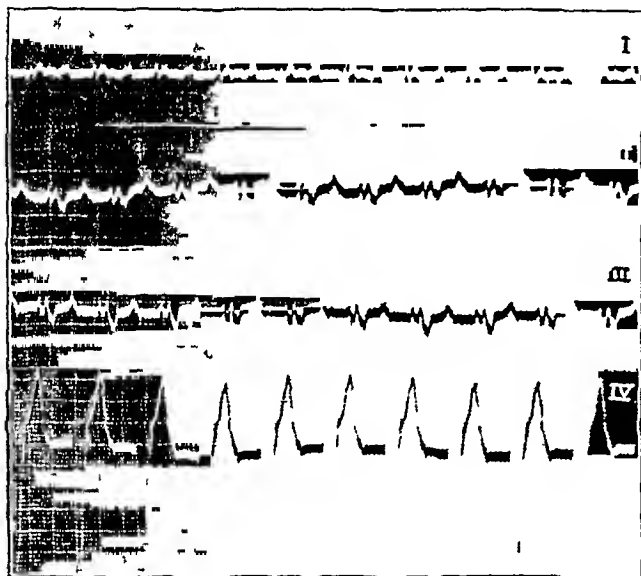


Fig 1—Electrocardiogram made on April 12, 1943, four days before death, showing abnormalities detailed in the text.

being palpable 2 cm beyond the left nipple line. In the apical and pulmonic areas the first heart sound was reduplicated but valvular murmurs were not heard. Both lungs were dull to percussion at the bases, and fluid was detected in the abdomen. The margin of the liver was felt at the level of the umbilicus, and there was tenderness to palpation in the right upper quadrant of the abdomen. The spleen and other viscera were impalpable. Pitting edema extended from both lower extremities over the vulva and the sacral area.

The urine contained a trace of albumin. The hemogram was normal. Intradermal tuberculin tests and Kahn tests of the blood elicited negative reactions. Aerobic and anaerobic cultures of blood yielded no growth. Roentgenography revealed cardiac enlargement toward the left, the right margin of the heart was indistinct because of increased radiopacity in the lower right pulmonary field. Throughout the upper part of the right and the entire left pulmonary field there was a notable increase in detail. The electrocardiogram showed regular rhythm, a ventricular rate of 90 per minute, auriculoventricular conduction time of twenty-four to twenty-six hundredths second, left preponderance,





Fig 2—Photograph showing the right side of the heart and the tricuspid valve. The pericardium and tricuspid valve are normal. The chambers are dilated and the walls hypertrophied. The cut edge of the myocardium is mottled with irregular gray areas of fibrous scarring. The endocardium of the auricle shows uniform gray fibrous thickening, while that of the ventricle shows patchy thickening over the interventricular septum. Several small mural thrombi are visible between the pectinate muscles of the auricle, and a large thrombus mass is present at the apex of the right ventricle.



Fig 3—Photograph showing the left side of the heart and the mitral valve, which is normal. The endocardium of the auricle is uniformly thickened, while that of the ventricle shows similar thickening most pronounced over the flat atrophied trabeculae carneae of the anterolateral ventricular wall. Both chambers are dilated and hypertrophied. The cut edge of the ventricle is mottled with gray areas of fibrous scar tissue most prominent just beneath the endocardium.



Fig 4—Photograph showing the dilated and hypertrophied left ventricle with mottling of its cut edges by fibrous scar tissue. The mitral and aortic valves are normal, but the ventricular endocardium is thick and gray, especially over the septum and anterolateral wall of the ventricle. Several mural thrombi are visible between trabeculae carneae near the aortic conus and near the apex.



Fig 5—Photomicrograph at low magnification of an area of acute myocarditis. The infiltration of inflammatory cells extends between the swollen granular muscle fibers. In this field the endocardium is only slightly affected.

thrombi were found between the pectinate muscles of the right auricle, in the tip of the left auricular appendage and between the trabeculae carneae of both ventricles. The coronary arteries were regular in diameter and perfectly patent. The aorta showed fatty streaks in the abdominal portion. Except for distention of veins throughout the systemic and portal systems, no abnormalities of the blood vessels were detected.

The right and left pleural spaces contained 700 and 250 cc respectively of slightly cloudy yellow fluid. The right lung weighed 370 Gm and the left 225 Gm. The external surfaces and the cut surfaces were dark bluish red, and the consistency of the parenchyma was firmer than usual in all areas. The middle lobe of the right lung and the lower lobe of both lungs were almost

Both ovaries showed small irregular dark red areas on the surfaces. No abnormalities were noted in any other organ.

**Microscopic Examination** Many sections were taken from the walls of all the chambers of the heart, these were stained with hematoxylin and eosin and various special stains (including Mallory's stain for connective tissue, Verhoeff's stain for elastic tissue, sudan III, Glynn's stain for bacteria and Custer's stain for granules). No section was free from lesions, although the appearance varied greatly in different sections and in different fields of any single section. The simplest lesions were widespread irregular areas of hydropic degeneration of heart muscle fibers. In cross sections the endomysial sheath was distended and contained a

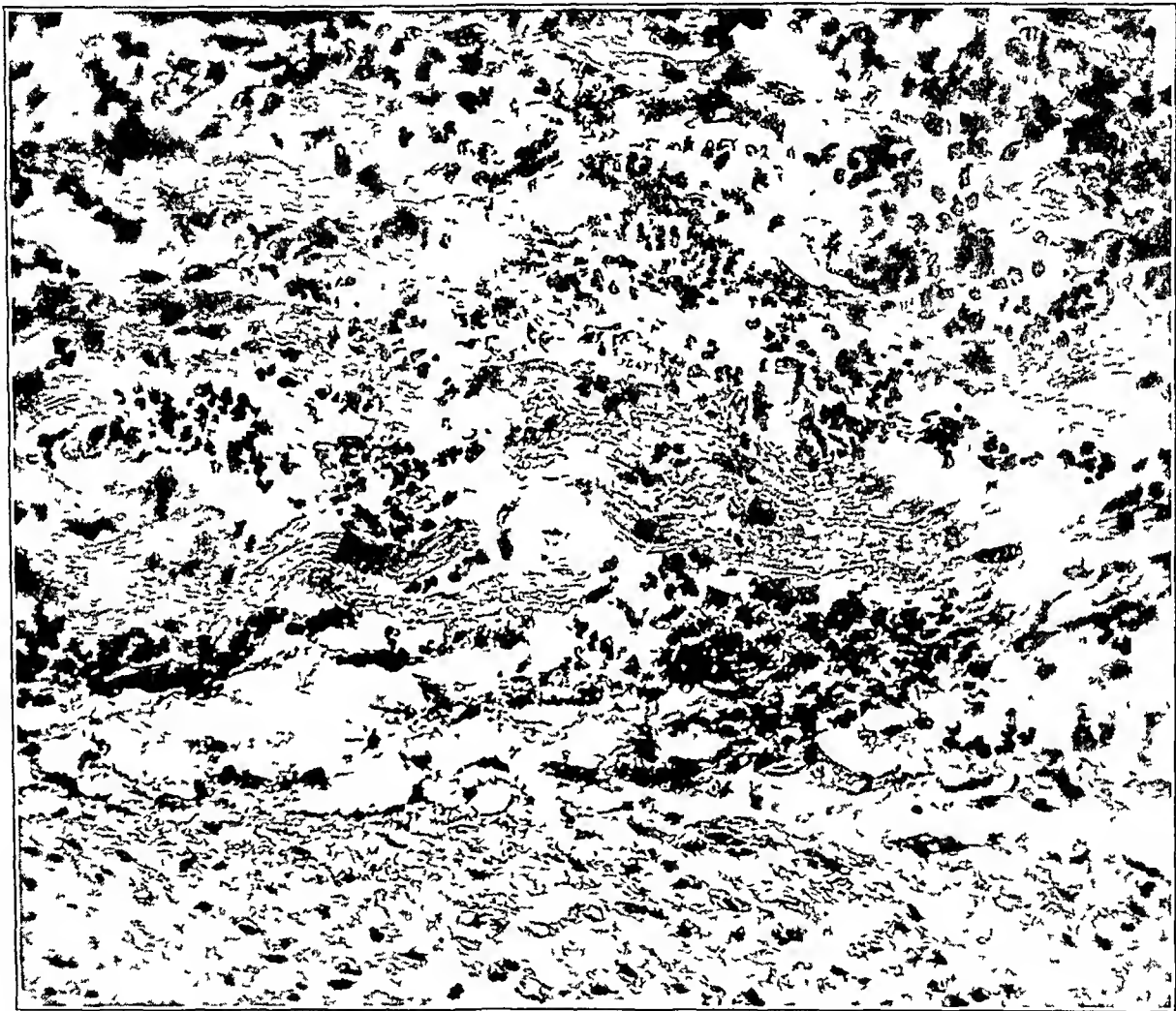


Fig 6—Photomicrograph at high magnification of an area of acute myocarditis, showing degenerative and early necrotic changes in the muscle fibers and an interstitial infiltration of polymorphonuclear leukocytes and red blood cells. There is striking proliferation of fibrous tissue in the adjacent endocardium (below).

hard, and each presented several large wedge-like dark red areas which tended to bulge slightly on the external surfaces. No occlusive lesions were found in any pulmonary vessel. The bronchial mucosa, although smooth and glistening, was rather red. The peritoneal cavity contained 1,000 cc of slightly turbid yellow fluid. The liver extended several fingerbreadths below the costal margin, weighed 900 Gm and had the characteristics of "nutmeg liver" to a marked degree. The spleen weighed 100 Gm, it was dark blue, exuded only a little dark red blood and retained its shape when sectioned. The right kidney weighed 90 Gm and the left 80 Gm. Their capsules stripped readily, perfectly smooth surfaces being left. Section revealed hyperemia accentuating the corticomedullary boundaries

large clear space, at the center of which a swollen, pale, rounded nucleus or a shrunken, angular, pyknotic one was often seen. In less degenerate fibers the myofibrils were clumped together so as to give a coarsely granular appearance. Tangential and longitudinal sections of muscle fibers showed cross striations even when severely affected. Another variety of lesion (figs 5 and 6) consisted of small focal areas of acute inflammation characterized by pronounced exudation of neutrophilic polymorphonuclear cells and red corpuscles, in these areas edema and hyperemia were severe, and the muscle fibers stained with variable intensity, some appearing necrotic. Eosinophilic leukocytes were rarely encountered, and lymphocytes, macrophages and multinucleated giant cells were entirely absent. Special stains

for bacteria failed to reveal any organisms in these areas on careful search. Almost every section contained one or more irregular areas wherein myocardial fibers were replaced by rather dense collagenous tissue. Occasionally an engorged capillary associated with small groups of neutrophilic leukocytes, lymphocytes and rare macrophages was encountered in these areas (fig 7), usually, however, the scars were strikingly acellular (fig 8). Often a few bundles of myocardial fibers were present in the midst of such a chronic lesion, of the individual fibers, some were noticeably hypertrophic while others were equally atrophic. The nuclei of the hypertrophic fibers were enormous, but neither were multinucleated cells found in any of these lesions, nor was there any necrosis. The areas of most abundant

proliferation. However, there was no significant degree of narrowing of the lumens.

Microscopic sections of the lungs showed chronic passive hyperemia with extremely large numbers of red cells and masses of amorphous eosinophilic granular material filling the alveoli of many lobules. Large macrophages were numerous in the alveolar spaces and in the bronchovascular supporting tissues, many contained brown granular pigment, and others were strikingly vacuolated. Perls' reaction was strongly positive for hemosiderin, and sudan III showed the vacuolation to be caused by fat globules. In such areas there was a tendency for fibroblasts to grow into the intra-alveolar masses. The bronchioles showed a mild chronic inflammation, with thick basement membranes. There was

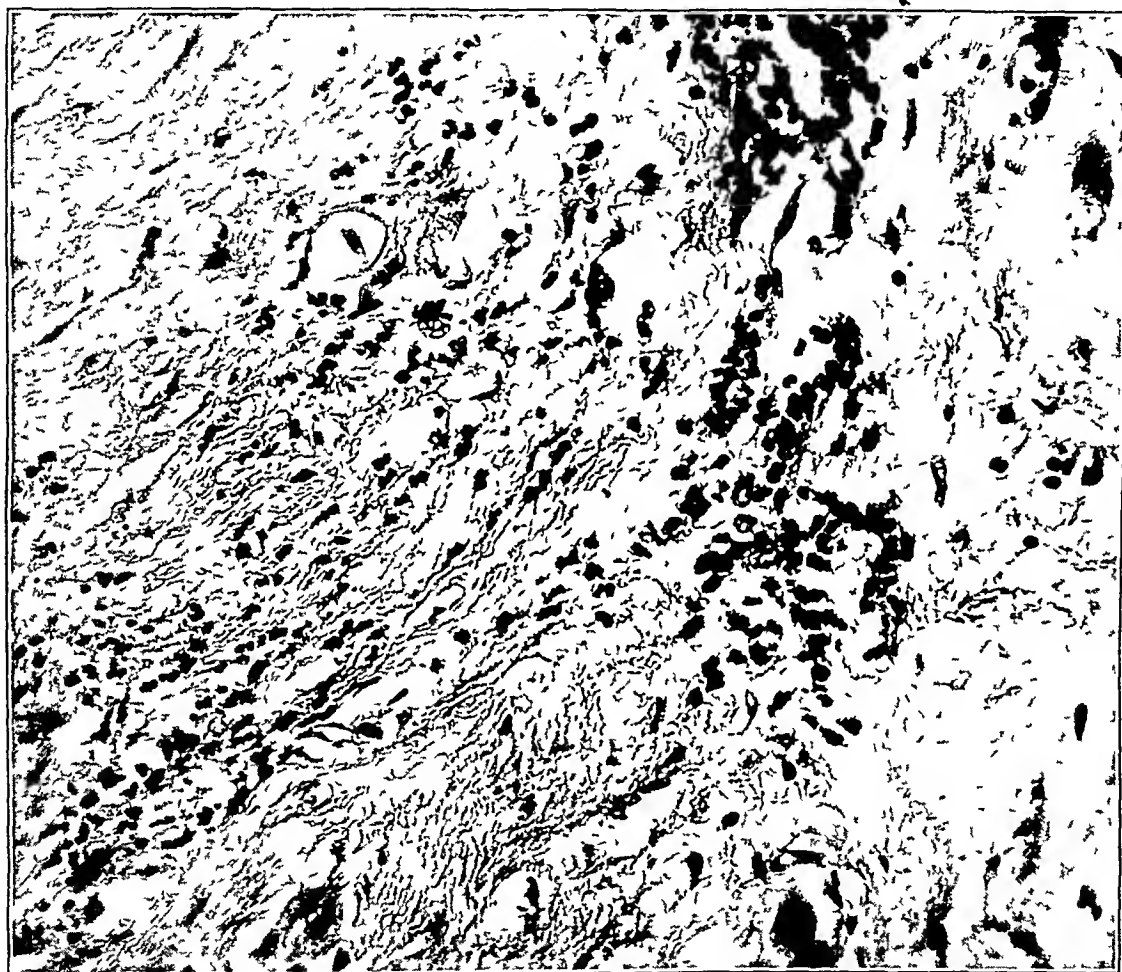


Fig 7—Photomicrograph at high magnification of a subacute inflammatory lesion in the myocardium. The inflammatory infiltration is composed of polymorphonuclear leukocytes and lymphocytes. Multinucleated giant cells are lacking. There is replacement by fibrous scar tissue of all but a few degenerate and atrophied myocardial fibers.

scarring were situated in the inner third of the myocardium and frequently involved the endocardium also. In every instance, however, such endocardial lesions, whether of acute or of chronic character, were related to underlying myocardial ones. By no means all of the endomyocardial lesions were associated with mural thrombosis, such thrombi as were found grossly were well organized at their points of attachment. Masses of granular calcium had been precipitated within the structure of the largest thrombus (near the apex of the right ventricle). Sections of the valves demonstrated their integrity. In all sections small branches of the coronary arteries were intact and patent, in larger branches and in both main coronary arteries the intima showed an unusual degree of loose cellular

no evidence of occlusion of pulmonary vessels. The liver showed severe chronic passive hyperemia and contained several small necroses surrounded by an exudate composed of polymorphonuclear leukocytes. The spleen and pancreas showed chronic passive congestion, the adrenal glands were hyperemic. Pronounced cloudy swelling and hyperemia were the only alterations of the kidneys. No significant lesions were seen in the sections of any other organs, including those of the brain.

**Pathologic Diagnosis.** The diagnoses were diffuse isolated myocarditis, diffuse fibrosis of the myocardium, hypertrophy and dilatation of the heart, mural thrombi of the heart (all chambers), chronic passive hyperemia of the lungs, liver, pancreas and spleen, anasarca,



ascites, bilateral hydrothorax, malnutrition, chronic bronchitis, slight lipid pneumonia, fatty streaks of the aorta, pediculosis capitis

#### COMMENT

The widespread myocardial lesions which have been described were undoubtedly responsible for the death of this patient from heart block and ventricular fibrillation. Although mural thrombi were present in all chambers of the heart, no evidence of pulmonic or systemic embolization was discovered. The mild chronic bronchitis and slight lipid pneumonia could scarcely have

dence of valvular endocarditis. Cultures of blood and staining of sections of the heart for bacteria did not reveal their presence, and there were no metastatic pyemic lesions in any organ. The patient's response to intradermal injection of tuberculin was negative, and there was no pathologic lesion suggestive of tuberculosis anywhere. The Kahn reaction of the blood was negative, and there was no clinical or pathologic evidence of congenital or acquired syphilis. Moreover, the myocardial lesions were not granulomatous. Viral, protozoal and helminthic

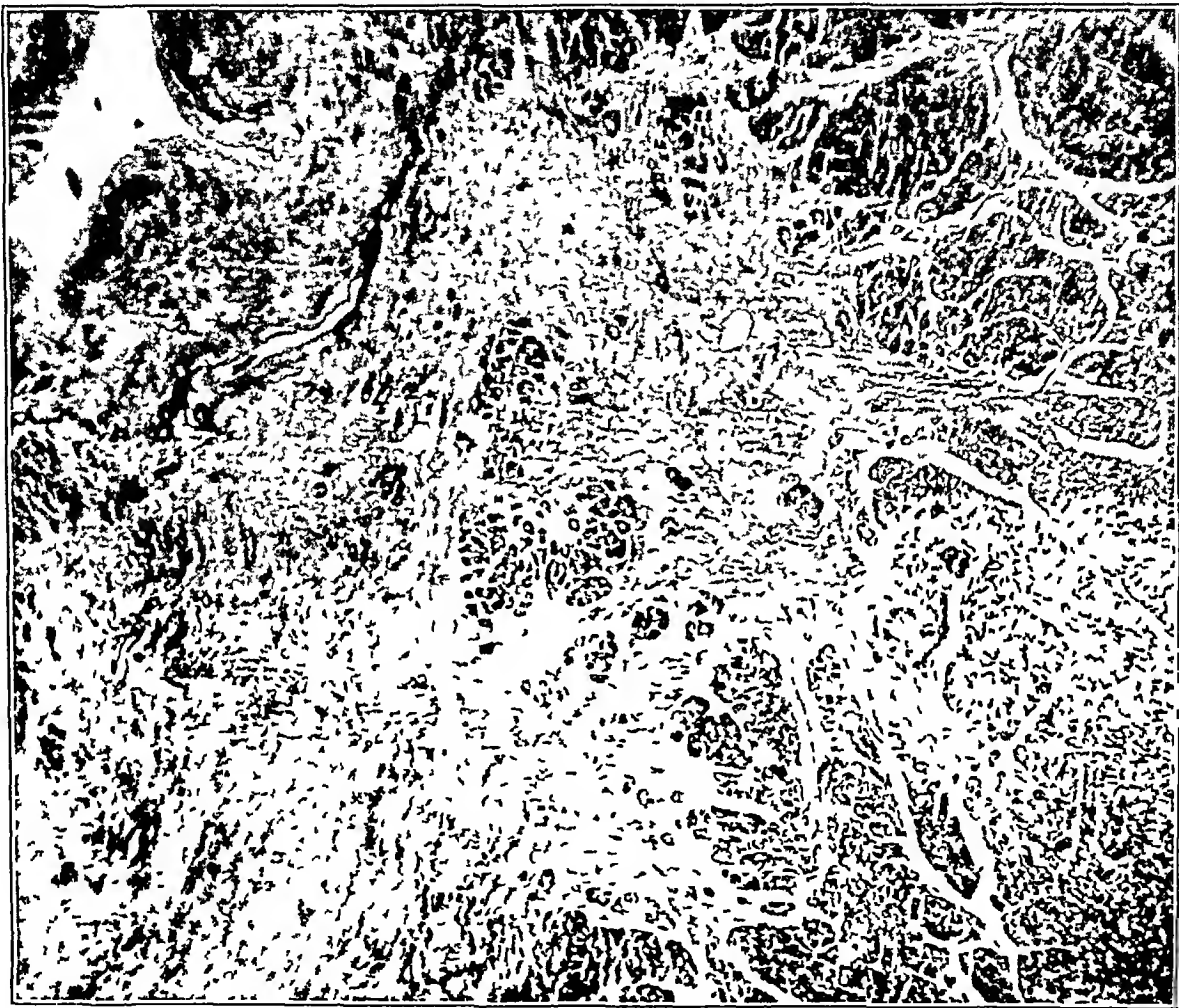


Fig 8—Photomicrograph at low magnification of a large irregular area of scarring in the inner third of the myocardium. Inflammatory cells are extremely few. Some of the remaining muscle fibers enclosed in scar tissue show hypertrophy, others are atrophied.

been responsible in any immediate way for death. All other pathologic conditions were consistent with chronic progressive myocardial insufficiency.

The unusual character of the myocarditis is obvious. None of the usual causes of myocarditis could be detected from the clinical or pathologic studies. The patient had never had any of the common infectious diseases of childhood. Neither the clinical nor the pathologic studies revealed conditions suggestive of rheumatic heart disease. Although there was extensive mural endocardial involvement in areas overlying myocardial lesions, there was no evi-

agents could not be even inferentially incriminated. Thyroid disease, uremia, poisoning with various chemicals, burns and serum sickness are occasionally accompanied by slight inconstant and variable alterations in the myocardium, but none of these conditions had ever been experienced by this patient. Periarteritis nodosa may be excluded because of the absence of inflamed or appreciably narrowed blood vessels from all the tissues examined. No sulfonamide compounds were ever given to this patient so far as could be determined, hence the possibility that the lesions represent an extraordinary example of the interstitial myocarditis described by

French and Weller<sup>6</sup> following the use of sulfonamide compounds is, at best, remote. Furthermore, the paucity of eosinophilic polymorphonuclear leukocytes in the more acute lesions and the advanced chronicity of many lesions constitute a dissimilarity to the myocarditis described by them. Disseminated lupus erythematosus may involve the heart muscle as well as the endocardium, but the dermal and systemic features of that disease were lacking in this instance. Thus, all known causes of myocarditis having been excluded and the absence of any major pathologic condition involving the endocardium, the pericardium or any other portion of the body having been determined, the myocardial disease described may be classified as diffuse isolated myocarditis.

As one considers the possible etiologic factors in this case, three outstanding features are notable: the weeping eczema during infancy, the presence of chronic tonsillitis and bronchitis with slight lipid pneumonia and the prolonged period of malnutrition.

The first deserves mention because the literature contains several reports of isolated myocarditis occurring in patients who were being treated with arsenical drugs for syphilitic dermatitis and with sulfur preparations for exfoliative dermatitis at the time of death. In the present instance nothing is known of the eczema except that after three years it disappeared entirely, leaving the patient in apparently unaltered good health.

The second feature is reminiscent of Franz's case<sup>7</sup> of an elderly woman who had received injections of epinephrine hydrochloride for bronchial asthma over a period of many years. Such cases caused Saphir<sup>2</sup> to remark that the common etiologic factor suggested by them is a peculiar hypersensitivity to the drugs or chemicals used in treatment. The respiratory conditions of the present patient, however, were never so treated, hence, they would seem to have played no more than an incidental role.

The third feature, malnutrition, has not often been reported. The cases of Lindberg<sup>3</sup> and of Smith and Furth<sup>5</sup> have been mentioned. Most accounts of beriberi heart describe dilatation of the right chambers of the heart, especially of the pulmonary conus, and microscopic changes which, according to Weiss and Wilkins,<sup>8</sup> are neither constant nor characteristic. Recent re-

ports of experimental thiamine deficiency give rather confusing observations. Follis, Miller and Wintrobe<sup>9</sup> found cardiac dilatation without hypertrophy and focal and diffuse myocardial necrosis in pigs dying of thiamine deficiency, in animals which had passed through several episodes of severe thiamine deficiency, scars marking healed necrotic lesions were found. The similarity of the lesions to those in some cases of Fiedler's myocarditis was pointed out. By utilizing a diet adequate in all known respects except for an extremely low content of potassium, Follis, Orent-Keiles and McCollum<sup>10</sup> produced in rats necrosis of myocardial fibers followed by scarring. Later, Follis<sup>11</sup> was able to prevent the development of such necroses by feeding diets which were also deficient in thiamine. Thomas, Mylon and Winternitz<sup>12</sup> studied vitamin B and potassium deficiency in rats and hogs. They found myocardial lesions characterized by necrosis of muscle fibers and pronounced cellular infiltration, no evidence emphasized one or other factor as primarily requisite for cardiac injury. Further investigation showed that deficiency of vitamin B<sub>6</sub> when coupled with deficiency of potassium produced cardiac damage in rats but that deficiencies in either thiamine or riboflavin together with potassium deficiency produced no significant changes. It is noteworthy that Follis and co-workers<sup>9</sup> found no pathologic changes in the hearts of pigs killed at a time when no clinical or chemical evidence of thiamine deficiency was demonstrable or in animals dying as a result of other types of vitamin deficiency or in animals in which inanition alone was produced. Sykes and Alfredson<sup>13</sup> found electrocardiographic abnormalities in calves fed for long periods on diets deficient in potassium, and Sykes and Moore<sup>14</sup>

8 Weiss, S, and Wilkins, R W. The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), *Ann Int Med* **11** 104, 1937.

9 Follis, R H, Miller, M H, Wintrobe, M M, and Stein, H J. Development of Myocardial Necrosis and Absence of Nerve Degeneration in Thiamine Deficiency in Pigs, *Am J Path* **19** 341, 1943.

10 Follis, R H, Orent-Keiles, E, and McCollum, E V. Production of Cardiac and Renal Lesions in Rats by a Diet Extremely Deficient in Potassium, *Am J Path* **18** 29, 1939.

11 Follis, R H. Myocardial Necroses in Rats on a Potassium-Low Diet Prevented by Thiamine Deficiency, *Bull Johns Hopkins Hosp* **71** 235, 1942.

12 Thomas, R M, Mylon, E, and Winternitz, M C. Myocardial Lesions Resulting from Dietary Deficiency, *Yale J Biol & Med* **12** 345, 1940.

13 Sykes, J F, and Alfredson, B V. Studies on the Bovine Electrocardiogram, *Proc Soc Exper Biol & Med* **43** 575, 1940.

14 Sykes, J F, and Moore, L A. Lesions of Purkinje Network of the Bovine Heart as a Result of Potassium Deficiency, *Arch Path* **33** 467 (April) 1942.

6 French, A J, and Weller, C V. Interstitial Myocarditis Following the Clinical and Experimental Use of Sulfonamide Drugs, *Am J Path* **18** 109, 1942.

7 Franz, G. Eine seltene Form von toxischer Myokardschädigung, *Virchows Arch f path Anat* **298** 743, 1937.



reported degenerative lesions in the Purkinje fibers of those calves, no lesions were found elsewhere in the myocardium. Various authors<sup>15</sup> have suggested that overtreatment of Addison's disease with adrenal cortex preparations might so lower the serum potassium level as to produce myocardial lesions similar to those found experimentally in studies of potassium deficiency, but references to such lesions have not been found. That potassium deficiency due to defective diet alone might occur in man seems unlikely in view of the widespread occurrence of that element in almost all foods consumed by man.

The existence of deficiency of any specific dietary factor in the present case cannot be proved, but the repeated diagnosis of malnutrition on the patient's several admissions to the hospital established beyond doubt the fact of an inadequate diet. Moreover, the patient's excellent response to high vitamin B intake, high caloric diet and other supportive measures during her second stay in the hospital further indicates the probability of vitamin deficiency. On her last admission the patient received large doses of thiamine intramuscularly and by mouth without noticeable benefit, this is contrary to the usual experience when the diagnosis of beriberi heart has been made. It is reasonable to suppose that a heart so badly damaged as that of the present patient could not respond in the usual satisfactory way. The acute and chronic noninfective myocarditis encountered in this case resembles closely the myocardial lesions of experimental thiamine or potassium deficiency as described by the investigators already cited. While there is no electrocardiographic or chemical evidence in the present case either favoring or denying the remote possibility of potassium deficiency, the

clinical evidence is such as to indicate not only the possibility but the probability of vitamin deficiency. Since it is possible to exclude with considerable certainty all of the other etiologic factors hitherto incriminated in cases of isolated myocarditis, there appear to be good grounds for casting something more than mere suspicion on deficiency of thiamine as the principal etiologic factor in the present instance of diffuse isolated myocarditis, since this is the one dietary factor deficiency of which has been shown experimentally to be capable of producing similar cardiac lesions.

#### SUMMARY

A 15 year old girl who had a history of prolonged malnutrition died of diffuse isolated myocarditis. Heart disease was known to have existed for at least six months before death. Severe failure of the right side of the heart was progressive, left bundle branch lesion, heart block and ventricular fibrillation preceded death.

The heart showed dilatation and hypertrophy, with acute, subacute and chronic, noninfective inflammatory lesions diffusely distributed throughout all parts of the myocardium. These lesions were most extensive in the inner third of the myocardium, and in places they encroached on the endocardium. Mural thrombi were found in both auricles and in both ventricles.

None of the etiologic agents usually incriminated in cases of isolated myocarditis was a factor in this instance. The possibility that the myocardial lesions may have been incited by prolonged dietary deficiency is suggested by the history of prolonged malnutrition and by the resemblance of the lesions to lesions experimentally produced as described in recent literature. Deficiency of thiamine is particularly suspected.

Dr G. Lyman Duff assisted in the study of this case and in the preparation of the manuscript.

<sup>15</sup> Ferrebee, J. W., Ragan, C., Atchley, D. W., and Loeb, R. F. Desoxycorticosterone Esters. Certain Effects in the Treatment of Addison's Disease, *J. A. M. A.* **113** 1725 (Nov. 4) 1939. Folliot<sup>11</sup>

# FATAL SPONTANEOUS POTASSIUM INTOXICATION IN PATIENTS WITH UREMIA

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Cardiac arrest due to an increase in the potassium of the serum to toxic levels has not been demonstrated in uremic patients who have maintained a large volume of urine up to the time of death. On the other hand, it has been shown that such arrest does occur regularly in dogs with ligated ureters<sup>1</sup>. Cardiac arrest by the action of potassium was also observed in 2 patients with oliguria and anuria complicating severe nephritis<sup>2</sup>. One of these patients had spontaneous elevation of the potassium of the serum to a level almost as high as that present at death. As each patient had received additional potassium salts, it was not possible to attribute death exclusively to the type of spontaneous potassium intoxication observed in dogs with experimental anuria.

In the cases to be described here potassium intoxication resulted from oliguria and failure of renal excretion. No potassium was given other than that contained in the diet and in the blood which was transfused into the first patient. The second patient did not have a blood transfusion and took no food during the week before death. For each patient the electrocardiograms and the levels of potassium of the serum immediately before death were comparable to those previously observed in association with fatal potassium intoxication in dogs<sup>1</sup> and in man<sup>2</sup>.

## REPORT OF CASES

**CASE 1—History**—A housewife aged 24 entered the hospital because of nausea and vomiting. Eleven years before, after an appendectomy, a diagnosis of renal ptosis was made and fixation of the left kidney carried out at another hospital. A month later, and repeatedly thereafter, a perirenal abscess was drained from the left flank. In the intervals between recurrences of the abscess there was continued pyuria, but the patient was otherwise well. Three weeks before admission a

From the Medical Clinic of the Peter Bent Brigham Hospital, and the Departments of Medicine and Pharmacology of the Harvard Medical School.

This work was done under the auspices of the University Committee on Pharmacotherapy.

<sup>1</sup> Hoff, H E, Smith, P K, and Winkler, A W. The Cause of Death in Experimental Anuria, *J Clin Investigation* 20:607 (Nov) 1941.

<sup>2</sup> Finch, C A, and Marchand, J F. Cardiac Arrest by Action of Potassium, *Am J M Sc* 206:507 (Oct) 1943.

cystoscopic examination was performed at a local hospital because of sudden hematuria. The retrograde pyelogram of the right side appeared normal, but a catheter could not be inserted in the left ureter, and phenolsulfonphthalein was not excreted by either kidney. After another recurrence and drainage of the abscess, the patient returned home, but suffered from epistaxis and increasing dyspnea with palpitation. Two days before the present admission pain appeared for the first time in the right costovertebral angle. This was accompanied by nausea, vomiting and abdominal distention. There was severe headache with vertigo. The face, hands and feet became swollen, and there was pronounced oliguria, with dark urine.

**Examination**—The patient appeared ill and confused. Respirations were rapid and deep, and the breath was urinous. The mucous membranes were pale, and the skin was yellow, dry and scaly. There were pitting edema to the waist and puffiness of the face and hands. Only minimal changes were present in the optic fundi. The lungs were free from rales. The heart was enlarged. A loud, blowing systolic murmur was heard at the apex. The systolic blood pressure measured 130 mm of mercury and the diastolic 100 mm, and the venous pressure was 150 mm of water. The abdomen was distended, and a draining sinus was present in the left flank. The neurologic examination revealed nothing abnormal save for a weakly positive Chvostek sign.

**Laboratory Data**—During eleven days in the hospital the hemoglobin (method of Schales) increased from 62 to 69 Gm per hundred cubic centimeters, after transfusions. The white blood cell count ranged from 7,000 to 13,000. The blood smears and differential counts were not remarkable. The urea nitrogen of the blood rose from 107 to 166 mg, and the nonprotein nitrogen from 155 to 208 mg, per hundred cubic centimeters. The protein content of the serum increased from 7 to 79 Gm per hundred cubic centimeters. On the fourth day it was 66 Gm, of which 29 Gm was albumin and 37 Gm globulin. The fasting blood sugar was 143 mg per hundred cubic centimeters. The carbon dioxide content of the plasma ranged from 129 to 215 millimols per liter, and was 159 millimols per liter on the day of her death. On the second day the calcium of the serum was 4.5 milliequivalents per liter, the phosphorus, 3.3 millimols per liter, and the sodium, 129 milliequivalents per liter. Five specimens of urine were collected. The reaction was alkaline, the specific gravity was 1.010, the reaction for albumin was 3 plus, and many red and white cells and occasional casts were present. A heavy growth of *Bacillus coli* was cultured from the urine, and a mixed growth of *Staphylococcus aureus* and *Streptococcus haemolyticus* B was obtained from culture of material from the wound in the left flank.

**Course**—The oral temperature reached 100 F during the first week and then fell. The pulse rate remained

near 100 a minute, and the respiratory rate decreased from 30 to 20 a minute. The blood pressure did not change appreciably. An electrocardiogram on the second day was normal except for low voltage (fig 1 A). There were continued nausea, vomiting, restless-

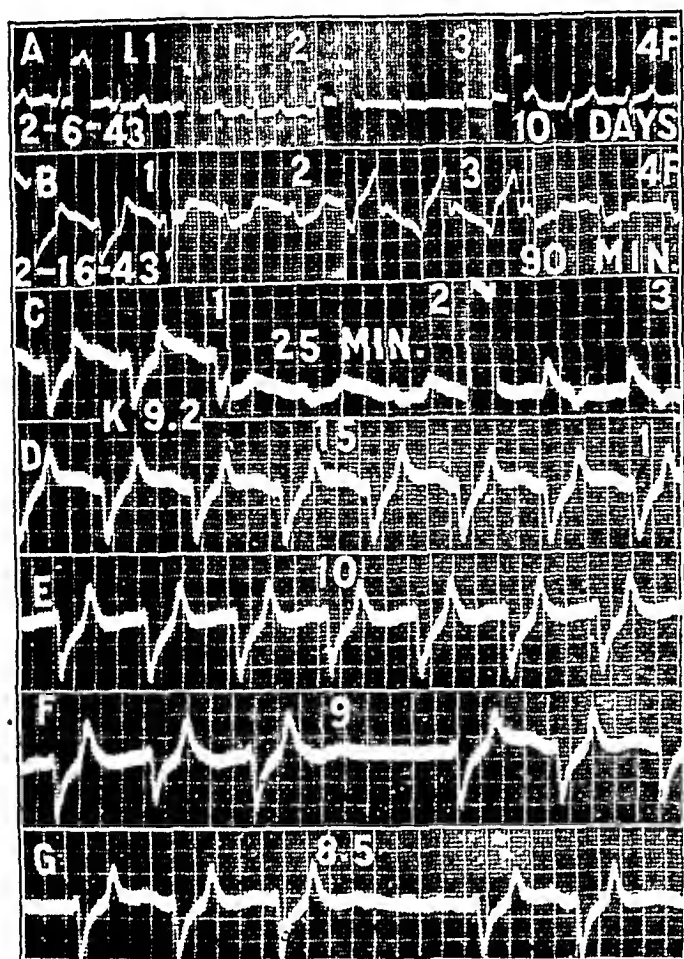


Fig 1 (case 1)—Electrocardiographic changes preceding cardiac arrest by action of potassium poisoning. Ten days before death tracings from the standard leads were normal except for low voltage (A). An hour and a half before death intraventricular block was pronounced, with curves of the right bundle branch block type, and the heart rate was 94 a minute (B). A continuous tracing recorded a succession of changes, arrest of the auricles, with loss of P waves and persistence of regular rhythm (C, D and E), a dropped beat (F), and, finally, increasing intervals of asystole, during which the complexes appeared in groups of two or three (G).

In this figure, and in the accompanying figures, the initial tracings were recorded on a Sanborn "Cardiette," and the continuous electrocardiograms, on an apparatus designed by Dr W B Likoff, graduate assistant in medicine at the Peter Bent Brigham Hospital, and Mr M B Rappaport, research engineer, Sanborn Instrument Co, Cambridge, Mass (Am Heart J, to be published). Each full strip on the figure represents six seconds. Standardization of deflections A and B, 1 cm = 1 millivolt, C to G, 2 cm = 2 millivolts. On each record, the number of the lead is in the upper right corner, and the time before death, at the center.

ness and confusion. Peripheral edema slowly increased, and bilateral hydrothorax and pericardial effusion developed. Involuntary twitching of the extremities occurred during the last four days of life. Digitalis was given, together with small amounts of dextrose and isotonic solution of sodium chloride by intravenous injection. With increasing edema and evidence of pulmonary con-

gestion, injection of the saline solution was discontinued, and thereafter, for six days, the fluid intake by mouth amounted to about 1 liter a day. A total of 280 cc of blood was given in four small transfusions, each transfusion being terminated by an attack of dyspnea and substernal oppression. The output of urine averaged 70 cc a day for five days, it then decreased and was virtually zero for three days. On the last day the patient became apprehensive and said she was dying. The twitching had increased, and she stated that she "felt funny all over." Although restless, she could remain quiet during examinations and was able to follow instructions. The eyes were prominent and rolling, and there were variations in the level of awareness. Consciousness was not lost until a few moments before death, when the heart beat had become infrequent and irregular. Respiration continued beyond the time when effective cardiac contractions occurred, and it ceased as a result of pulmonary edema two minutes before the final cessation of cardiac activity. The continuous electrocardiogram showed a three minute period of restoration of regular rhythm, accompanied by a palpable peripheral pulse, forty-four seconds after the beginning of a slow intravenous injection of calcium gluconate (figs 1, 2 and 3).

**Autopsy**—The heart weighed 460 Gm. It had stopped in diastole and was distended with blood. There were a thick, yellow, fibrinous deposit on the visceral and the parietal pericardium and an effusion of 400 cc of clear reddish fluid in the pericardial sac. A postmortem

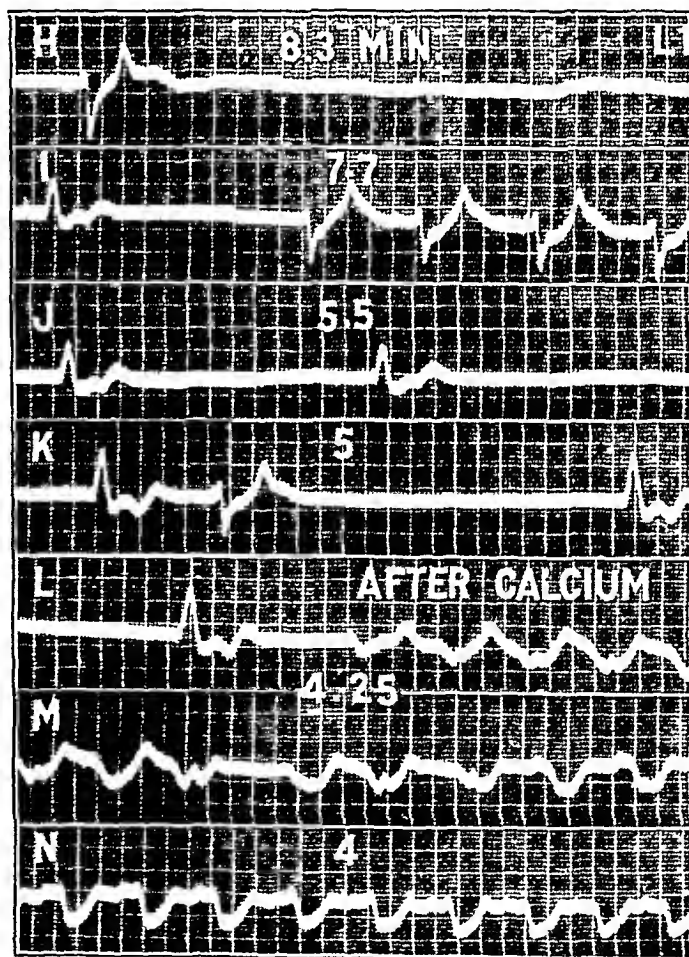


Fig 2 (case 1)—Effect of calcium (lead I). The periods of asystole increased to as long as nine seconds, and the duration of the complexes was greatly prolonged (H). The direction of the complexes varied with changes in the degree of block in conduction on the two sides of the heart (I, J and K). Regular rhythm was resumed after the intravenous injection of calcium gluconate (L, M and N).

roentgenogram of the heart showed no intracardiac calcification, and microscopic sections showed no evidence of vascular disease or myocardial infarction. The lungs were edematous but not consolidated. Their respective weights were 680 and 520 Gm. The left kidney was small and inseparable from a mass of scar tissue adherent to the vertebrae. It was composed of multiple loculi of purulent and necrotic material, each one continuous with the draining sinus in the left flank. The remains of a dilated renal pelvis communicated with a ureter occluded by fibrous tissue near the hilus of the kidney. The right kidney weighed 300 Gm. The capsule stripped easily. On cut section it appeared blood streaked and edematous. Microscopic examination revealed subacute glomerulonephritis with involvement of all the glomeruli in varying degrees (fig 4).

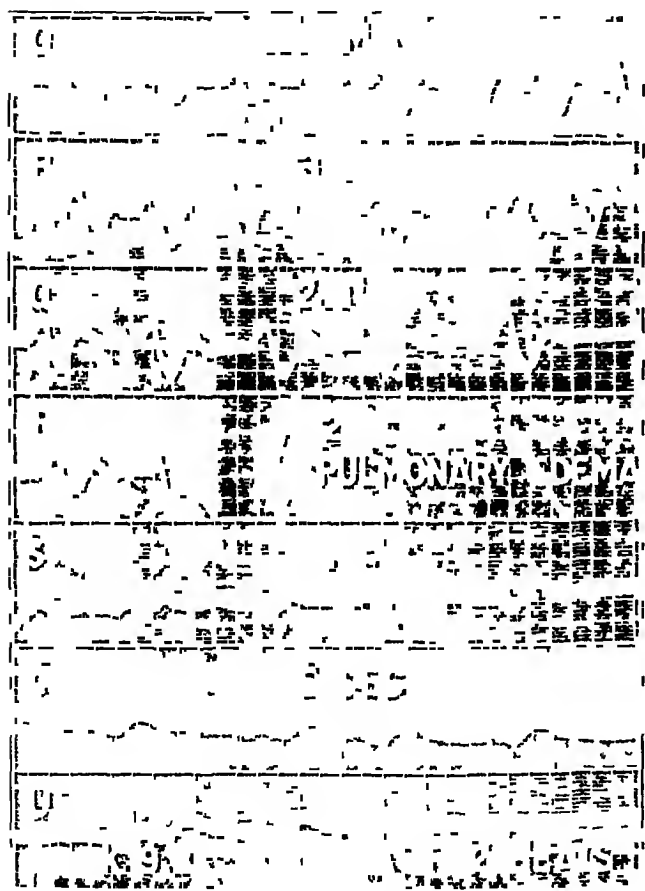


Fig 3 (case 1)—Final stages of arrest (lead I). The overlapping complexes (O and P) gave the appearance of a circus movement, but each impulse was actually separate, as seen in (Q), where the overlap was eliminated by slowing of the rate from 90 to 50 a minute. At the moment that pulmonary edema prevented further respiration there was struggling (R), followed by a few terminal microstokes (S and T) and final cardiac arrest (U).

**CASE 2<sup>3</sup>—History**—A labor union secretary, aged 41, entered the hospital because of drowsiness and headaches. Ten years previously he had passed a life insurance examination, at that time, however, he was beginning to feel below par, and a diagnosis of hypertension and Bright's disease was made at another hospital. Thereafter, he had had nocturia for several years, fre-

quent headache and vomiting for two years and failing vision, muscular twitching and decline in weight, from 235 to 178 pounds (106.6 to 80.7 Kg), for six months. For a month he had also had episodes of dyspnea on exertion, paroxysms of nocturnal dyspnea and occasional nosebleeds. The face appeared slightly puffy, and there was itching of the skin. Mental confusion became evident in the last week of life. At the time of admission there were epistaxis, of several hours' duration, headache and pain in the chest.

**Examination**—The patient was large and ruddy. He appeared drowsy and confused. The skin was telangiectatic over the cheeks and dry and yellow in general. A powdery scale was present about the eyes and over the arms. There was a stare characteristic of nephritis. In the optic fundi the nerve disks were elevated and indistinct. The retinal arteries were narrow and tortuous and compressed the veins at intersections. There were retinal scars, patches of exudate and hemorrhages in all stages. Visual acuity was 20/200, and newsprint was not distinguished at close range. Dentition was poor, the tongue was brown and furry, and the mucous membranes were pallid. A few moist rales were heard over the lower posterior field of both lungs. The heart was enlarged, and the aortic second sound was loud and ringing. The blood pressure was 225 systolic and 190 diastolic. The abdominal organs were not palpable. There was muscular twitching of the extremities.

**Laboratory Data**—On admission the red cell count was 3,600,000, and the white cell count, 10,000 per cubic millimeter, with a normal differential count. The hemoglobin decreased in five days from 113 to 97 Gm per hundred cubic centimeters (Schaes). On the second day the nonprotein nitrogen of the serum was 258 mg per hundred cubic centimeters, and the total protein, 74 Gm per hundred cubic centimeters, of which 38 Gm was albumin and 36 Gm globulin. The urea nitrogen of blood on the fifth day measured 163 mg per hundred cubic centimeters. The chloride of the serum was 96 milliequivalents per liter on the second day, the calcium of the serum measured 4 millimols per liter on the second day and 3.7 millimols on the fifth day. The specimens of urine were yellow and acid on the first three days and were alkaline and brownish or bloody thereafter. The specific gravity was fixed at 1.010, and the urine gave a 2 plus reaction for albumin and contained numerous red cells, a few white cells and rare hyaline or granular casts. There were occasional small blood clots.

**Course**—The patient lived ten days after admission but vomited repeatedly and was unable to take food. He was sufficiently lucid to recognize persons and converse until the last day, but was continually confused and restless. An electrocardiogram on the fourth day indicated a left axis deviation. The pulse rate was between 90 and 100 a minute, and the blood pressure remained constant. The respiratory rate was 20 a minute. The intake of fluid was between 1,100 and 1,600 cc a day, most of which was given as 5 per cent dextrose by clysis. The volume of urine averaged 660 cc a day for a week and then decreased to about half that amount. In the last four days the bladder was emptied by catheterization because of failure to void. During this interval there were periods of profound drowsiness, with intermittent respiration. Fourteen hours before death there was a uremic frost. A succession of changes appeared in the electrocardiogram (figs 5, 6 and 7), and the patient gradually lapsed into an unresponsive state, during which he squirmed about, fumbled with his hands and muttered repetitious syllables with each

<sup>3</sup> The study of this case was made possible through Dr. James P. O'Hare.



breath The Cheyne-Stokes respiration continued, but the blood pressure did not fall until increasing intervals of asystole had appeared on the electrocardiogram, just before final cardiac arrest In the last hours of life the heart sounds had become faint, prolonged and swishing The skin was moist, but there was no venous distention or edema Four minutes before the last electrical impulse was recorded no peripheral pulse could be felt, and the blood pressure could not be measured Respiration ceased two minutes later

The table gives values for potassium in the 2 cases

Results of Determinations of Potassium in Two Cases of Uremia\*

Source	Value mEq /L
Case 1	
Serum 20 min before death	9.2
Serum from heart blood at death	9.8
Spinal fluid at death	4.5
Pericardial fluid at death	9.0
Case 2	
Serum 6 days before death	5.8
Serum 13½ hr before death	8.8
Serum 3¾ hr before death	9.2
Serum from heart blood at death	10.1
Spinal fluid at death	4.5
Pericardial fluid at death	8.8
Urine 5 days before death	52.5
Urine 1 day before death	49.8
Urine from bladder at death	52.5
Total potassium excreted in urine	
315 cc 5 days before death	16.5 mEq (0.064 Gm) /24 hr
300 cc 1 day before death	14.9 mEq (0.058 Gm) /24 hr
65 cc last day of life	3.4 mEq (0.013 Gm) /11 hr

\* Specimens of blood were collected under oil, and the serum was separated at once. No hemolysis occurred. The analyses for potassium were made by Dr. A. W. Winkler, of the department of medicine Yale University according to Hald's modification of the chloroplatinate method of Shohl and Bennett (Hald, P. M. Determination of the Bases of the Serum and Whole Blood J Biol Chem 103: 471 [Dec.] 1933). To convert milliequivalents of potassium per liter to milligrams per hundred cubic centimeters the value for the former is multiplied by 3.9.

# COMMENT

In each of these cases the development of a high concentration of potassium in the serum was associated with failure of renal excretion sufficient to produce other evidence of azotemia as well. This was represented in the first case by the evidence of loss of chloride, sodium and calcium and by retention of phosphate and nitrogenous substances. The oliguria, and finally the anuria, of the last two weeks of life was the result of glomerulonephritis involving the remaining right kidney, apparently a complication of the infection with *Str. haemolyticus* B in the left flank. There was no indication of any toxic effect from potassium until after this interval of oliguria, and it is evident that there was no significant failure in excretion of potassium until after failure of water excretion had begun. Not even the earliest effect of an increase in the potassium of the serum, which is a heightening of the T wave,<sup>4</sup> had appeared until after the vol-

ume of urine had decreased. As extrarenal excretion of the substance is negligible, the failure of excretion of potassium was shown in case 1 by the progression from oliguria to virtually complete anuria and in case 2 by the presence in the urine of only a small fraction of the amount of potassium normally excreted by the kidney.

The three sources from which the high concentration of potassium in the serum appears to have been derived were (a) diet, (b) red cells introduced by transfusion of blood and (c) tissue metabolism. Of these, the last in itself has regularly sufficed to cause death of animals with experimental anuria.<sup>1</sup> There was no evidence that any unusual amount of intracellular potassium was liberated as a result of destruction of the patient's body tissues.

In the second case the elevated level of potassium appears to have been derived largely from tissue metabolism, since no transfusion was given and no food was taken in the last week of life. The course in this respect was comparable to that of anuric dogs which die of potassium intoxication even in the absence of any dietary intake. The course differed in that the suppression of potassium excretion was more gradual and there was no complete cessation of water excretion.

It has not been possible to demonstrate by chemical methods alone that potassium may be an actual cause of death from uremia in man. However, toxic effects from impaired excretion of potassium and the resulting high levels in the blood have been suggested by a series of observers, and the earlier data on the frequent tendency to retention of potassium in patients with renal disease have been currently reviewed and amplified.<sup>5</sup>

Symptoms attributed to high levels of potassium in the serum include the paresthesia and weakness which were experienced in case 1 and which have been reported to follow large oral doses of potassium salts.<sup>6</sup> There was no evidence that the persistent vomiting in the 4 reported cases of fatal potassium intoxication was caused by potassium, although the authors also observed vomiting in intact dogs killed by the slow intravenous infusion of solutions of potassium chloride. The flaccid quadriplegia which accompanied fatal potassium intoxication in 2 instances<sup>2</sup> did not occur in these cases, and the actual role of potassium in relation to such paralysis remains obscure. In each case a disturbance in the level of other electrolytes and metabolites in the blood also contributed to the symptoms,

5 Keith, N. M., King, H. E., and Osterberg, A. E. Serum Concentration and Renal Clearance of Potassium in Severe Renal Insufficiency in Man, *Arch. Int. Med.* 71: 675 (May) 1943.

4 Thomson, W. A. R. The Effect of Potassium on the Heart in Man, *Brit. Heart J.* 1:269 (Oct.) 1939.

and in the 2 cases cited here the tetanic effect of hypocalcemia may have counteracted any tendency to flaccid paralysis or loss of tendon reflexes

✓ Neither in experimental animals nor in man does the effect of potassium on the heart result in signs or symptoms of circulatory failure until

the sequence of electrocardiographic changes alone is sufficiently specific to serve as a basis for the selection of cases in which chemical studies should also be made. ✓

The significant features of the electrocardiograms shown here include elevations and rapid variations in the height of the T waves, changes

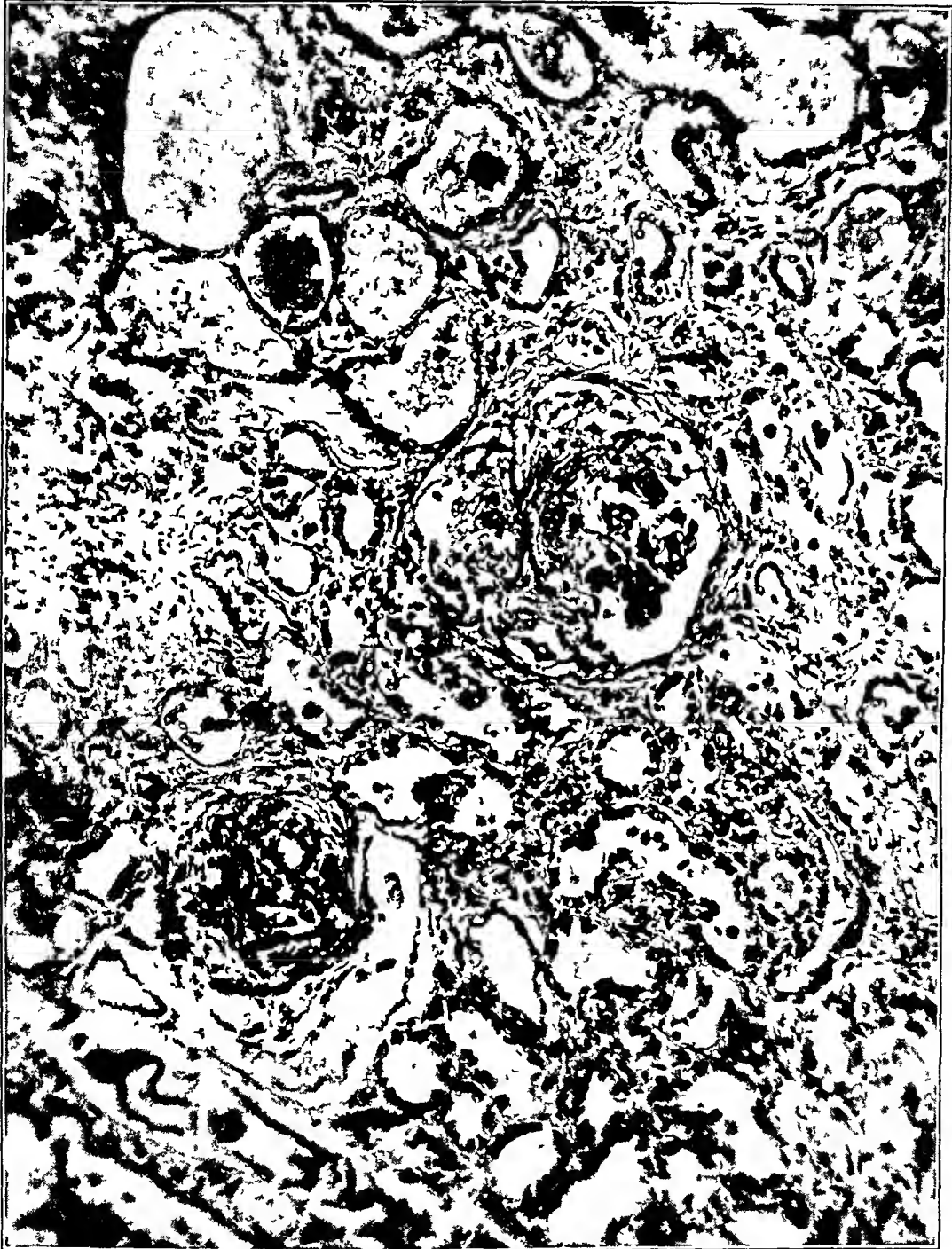


Fig 4 (case 1) —Right kidney There are numerous fibrous adhesions between the glomerular tufts and Bowman's capsule, as well as between individual tufts The tubules are separated by diffusely increased interstitial connective tissue The tubular epithelium is atrophic Varied amounts of precipitated protein are seen in the lumens Phloxine-methylene blue,  $\times 150$

just before cardiac arrest ✓ The diagnosis must therefore be established by a demonstration of the characteristic changes in the electrocardiogram, accompanied by sufficiently great elevation in the level of potassium in the serum ✓ However,

in the amplitude of the R waves and pauses representing momentary arrest of the sinoauricular node Shortly before final cardiac arrest there were loss of P waves, due to auricular arrest, idioventricular rhythm and a pronounced delay



of conduction in the ventricles, with variations in the relative degree of block on the two sides of the heart. The progression of block in ventricular conduction was associated with increase in the voltage of the deflections, elevation of the

the ventricular complexes increased in duration from three-tenths and four-tenths second respectively ten and six days before death to three-fourths second or more at the time of arrest. The changes in the standard leads (figs 1 *B* and *C* and fig 5) were of the type interpreted according to Wilson's criteria as evidence of right bundle branch block, but did not result from disease of the coronary arteries to which such changes are frequently attributed. Continued, but slow, circulation of the blood in the moment prior to cardiac arrest was shown in case 1 by the effect which became apparent forty-four seconds after the beginning of an intravenous injection of calcium gluconate. The calcium ions temporarily restored a regular rhythm and normal rate. Such electrocardiographic changes as would have resulted from the pericarditis with effusion were

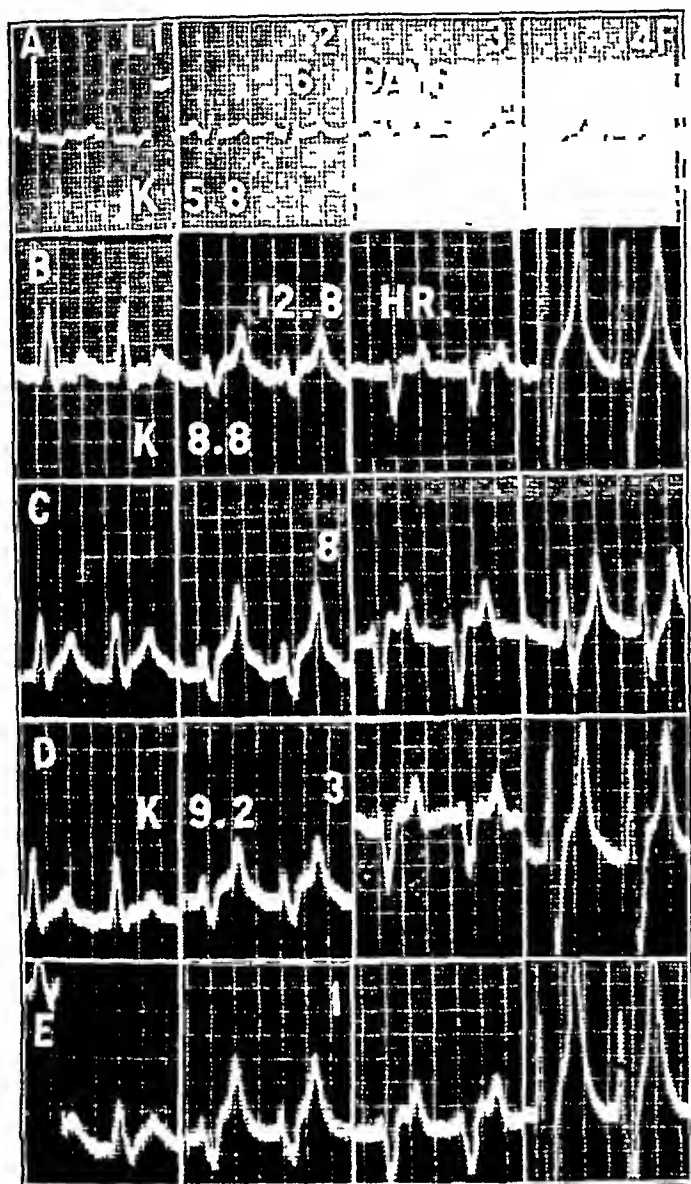


Fig 5 (case 2) —Serial electrocardiograms in a case of potassium intoxication. A control tracing of the four standard leads six days before death showed an inverted T<sub>1</sub> wave and left axis deviation (*A*). Changes in the fourteen hours preceding death (*B*, *C*, *D* and *E*) included the development of intraventricular block, with curves of the right bundle branch block type and a progressive increase in the duration of the individual deflections and the complexes as a whole. There were variations in voltage and a decrease in the amplitude of the R waves, accompanied by a notable increase in the height of the T waves. Deflections in lead IV finally exceeded the width of standard electrocardiograph paper. Auricular arrest is indicated by the gradual depression and loss of P waves.

In *A*, 1 cm = 1 millivolt, in *B* to *E*, 3 cm = 15 millivolts.

portion of the complexes derived from the T waves, displacement of the portions derived from the S-T segments, overlapping between successive complexes and between portions within the complexes and transition from sharp to smooth and flowing contours. Altogether, in these 2 cases

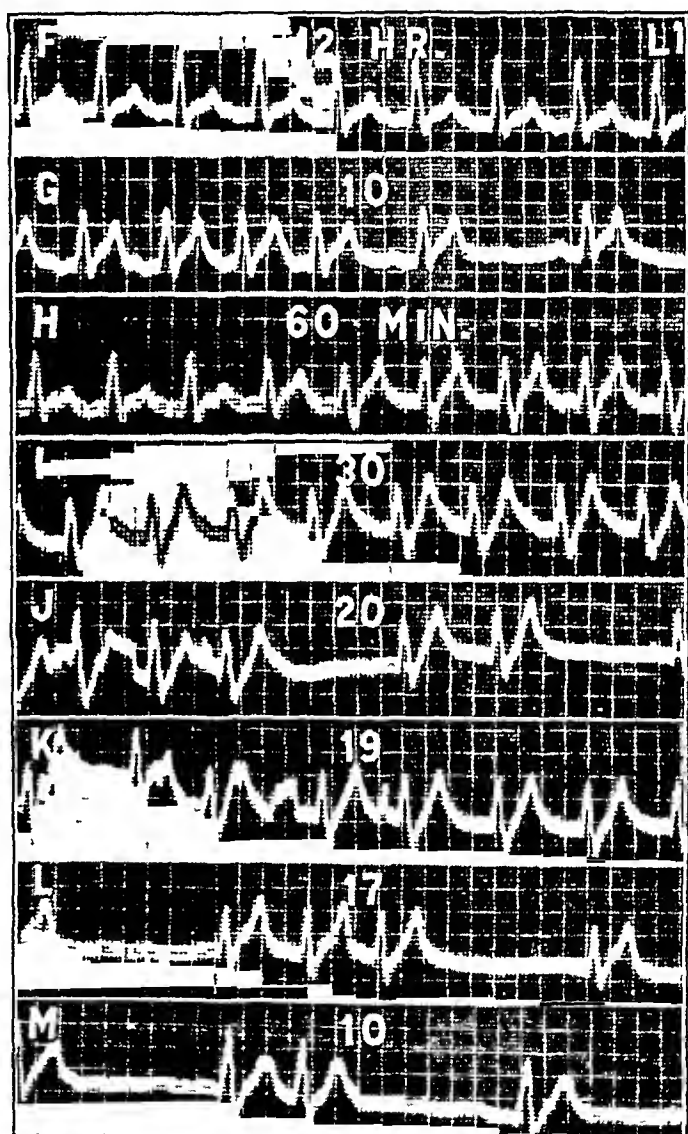


Fig 6 (case 2) —Stages preceding cardiac arrest. Lead I, in the last twelve hours of life, showed prolonged, overlapping complexes (*F*), momentary pauses of the sinoauricular node prior to auricular arrest (*G*), changing block, with rapid variations in the R, S and T waves (*H*), and an amplitude of the T waves finally exceeding that of the R waves (*I*). Twenty minutes before death there appeared increasing intervals of arrest, during which the P waves appeared to be depressed and then lost and complexes began to appear singly and in small groups (*J*, *K*, *L* and *M*).

entirely masked by the more striking effects of potassium intoxication

The concentrations of potassium in the serum of 9.8 and 10.1 milliequivalents per liter in the 2 cases represent an increase to an amount twice that normally present. This level is in the lower portion of the range of values at which cardiac arrest has been observed in experiments on dogs.<sup>1</sup> It may be compared with the previously reported level for man of 8.85 milliequivalents per liter reached spontaneously and 10.5 milliequivalents

from the levels for the serum but is higher than the amount ordinarily present

In 2 previously described cases of potassium intoxication,<sup>2</sup> and in the first of the 2 cases described here, consciousness was retained until immediately before death. Our second patient had become stuporous in his final hours, apparently as a result of administration of barbiturates. In all 4 cases an abrupt circulatory failure preceded the cessation of respiration and in the 3 cases in which autopsy was done the heart had stopped in diastole. In our last case the heart was sufficiently dilated to permit the collection of a large specimen of blood. The cause of the renal failure was severe nephritis in all but the last case, in which it was malignant nephrosclerosis. As there is no indication that potassium intoxication is a specific effect of these diseases, it may also be expected to occur in association with advanced renal failure from other causes.

#### SUMMARY

✓ Fatal spontaneous potassium intoxication occurred in 2 cases of uremia with renal failure and oliguria. The failure in excretion of potassium resulted in an increase in the concentration of potassium in the serum to 9.8 and 10.1 milliequivalents, while the concentration in the pericardial fluid was 9 and 8.8 milliequivalents and that in the spinal fluid 4.5 milliequivalents per liter at death. Serial electrocardiograms showed the characteristic changes leading to cardiac arrest by the action of potassium, including evidence of auricular arrest and progressive delay of conduction in the ventricles. The symptoms were those usual with uremia. Consciousness persisted up to the time of death in the first case, but became clouded in the second case. In the first case the intravenous injection of a solution of calcium gluconate resulted in transient restoration of regular rhythm. The cessation of respiration in each case was preceded by circulatory failure, and there was evidence that the heart was arrested in diastole. ✓

Dr Alexander Winkler made the analyses for potassium, and Dr William B. Likoff gave us the use of his continuously recording electrocardiograph.

Peter Bent Brigham Hospital

Fig 7 (case 2)—Arrest of heart (lead I). There was a momentary reappearance of P waves five minutes before cardiac arrest, at a time when the rhythm was regular and the rate 40 per minute (N). Maximal spreading is seen in the single and paired terminal complexes, which appeared at regular, but infrequent, intervals during the last minutes of life (O, P, Q and R). The last impulse continued as a circus movement for slightly over a minute before becoming exhausted (S, T and U).

per liter at death.<sup>2</sup> The 9 and 8.8 milliequivalents per liter for the pericardial fluid may represent a lower level for the serum while the effusion was forming. The level of 4.5 milliequivalents per liter for the spinal fluid in the 2 cases differs

6 Arden, F. Experimental Observations upon Thirst and on Potassium Overdosage, *Australian J. Exper. Biol. & Med. Sci.* **12**: 121 (Sept.) 1934. Keith, N. M., Osterberg, A. E., and Burchell, H. B. Some Effects of Potassium Salts in Man, *Proc. Staff Meet., Mayo Clin.* **17**: 49 (Jan. 28) 1942, *Ann. Int. Med.* **16**: 879 (May) 1942. Thomson.<sup>4</sup>

# VITAMINS A, B AND C IN DIABETIC CHILDREN

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The results of an investigation made in the summer of 1941 on the vitamin status of the diabetic children at the summer camp of the New York Diabetes Association have been reported<sup>1</sup>. In 1942 the observations were repeated because it was felt that the first effort was fragmentary and that a more satisfactory and complete survey could be accomplished with an increase in laboratory personnel and equipment and with improved methods. In the present paper the results obtained in the second study are reported.

## CLINICAL MATERIAL

One hundred and fourteen juvenile diabetic subjects from 6 to 18 years of age, except for 2 aged 20 and 26 respectively, were studied. They were about equally divided as to sex. The children came in four successive groups during July and August 1942, each group spending two weeks at the camp. They were largely patients of the diabetes clinics in Greater New York, though a few were referred by individual physicians. Except for diabetes they had no physical ailments. A medical history was taken of each child, in which were recorded the duration of the disease, the success achieved in control of the diabetes, the dose of insulin, the diet prescribed and the growth status. Daily checks were made on the urine, the physical condition, the diet and the dose of insulin while the child was at the camp. The data were then correlated with the results of the vitamin determinations. Eleven normal young adults, members of the camp staff, served as controls.

## METHODS

The clinical criteria for deficiency were those generally accepted. Vitamin A deficiency was diagnosed by inspection of the epithelial tissues (xerosis conjunctivae and keratosis pilaris). Thiamine (vitamin B<sub>1</sub>) deficiency was considered to be present if chronic fatigue, diminished intensity or absence of the ankle or the knee jerk, tenderness of the muscles of the calf or sensory disturbance (alteration in touch, pain or vibratory sense) was demonstrated, chronic fatigue alone was not regarded as warranting a diagnosis of vitamin B<sub>1</sub> deficiency. A riboflavinosis was revealed by the presence of scaly blepharitis, cheilosis or smoothness of the tongue, with or without denudation. The

From Camp Nyda, conducted by the New York Diabetes Association, Inc.

This study was aided by a grant from the Ella Sachs Plotz Foundation.

Mr Felix Morgenstern donated a photoelectric colorimeter for use in the determinations.

<sup>1</sup> Freston, J M, and Loughlin, W C. Vitamin Deficiencies in Diabetic Children, New York State J Med **42** 1833-1837 (Oct 1) 1942.

diagnosis of avitaminosis C on the basis of physical signs proved unsatisfactory. The adequacy of the Rumpel-Leede tourniquet test has been discredited in recent publications, in our experience the results of the test did not parallel the occurrence of "chemical scurvy". None of our patients had clinical evidence of scurvy. Gums which were swollen or bled easily were prevalent, and it was impossible to be certain whether poor dental hygiene or lack of vitamin C was responsible for these abnormalities.

The amounts of carotene and vitamin A were determined with the Klett-Summerson photoelectric colorimeter. The method was based on the Clausen-McCord extraction and the Carr-Price reaction, the modification by Sinay<sup>2</sup> will be published elsewhere. The specimens were protected from light from the time of venipuncture to the final reading. Four cubic centimeters of plasma was extracted, the carotene content determined, the extract dried under a stream of oil-pumped nitrogen and the amount of vitamin A estimated. Standardization curves were based on a series of concentrations of pure crystalline vitamin A and 100 per cent carotene (90 per cent  $\beta$ -carotene). A correction curve was used to compensate for any blue color in the final reaction due to carotene. The results were expressed in micrograms of carotene or vitamin A per hundred cubic centimeters of plasma.

The ascorbic acid levels of the plasma were determined titrimetrically according to the procedure of Farmer and Abt<sup>3</sup>. Two cubic centimeters of plasma was precipitated immediately with 6 per cent metaphosphoric acid, and the filtrates were stored at 5 C until titrated, about three hours later.

Cholesterol levels in the plasma were estimated by the Bloor extraction method,<sup>4</sup> with color development under temperature control as described by Ireland<sup>5</sup>.

## NORMAL VALUES

The carotene content of plasma ranged from 272 to 139 micrograms, with a mean value of 195 micrograms. The vitamin A level varied from 71 to 40 micrograms, with a mean value of 50 micrograms. The normal vitamin A-carotene ratio fell sharply between 0.28 and 0.21.

<sup>2</sup> Sinay, M W. Personal communication to the authors.

<sup>3</sup> Farmer, C J, and Abt, A F. Ascorbic Acid Content of Blood, Proc Soc Exper Biol & Med **32** 1625-1629 (June) 1935.

<sup>4</sup> Bloor, W R, and Knudson, A. The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J Biol Chem **27**:107-112, 1916.

<sup>5</sup> Ireland, J T. Colorimetric Estimation of Total Cholesterol in Whole Blood, Serum, Plasma and Other Biological Material, Biochem J **35**:283-293 (March) 1941.

The normal value for the ascorbic acid content of plasma is not finally established, we have accepted figures above 0.8 mg per hundred cubic centimeters of plasma as representative of tissue saturation and values between 0.8 and 0.4 mg as indicative of tissue unsaturation, a level of less than 0.4 mg has been regarded as critical, and as evidence of chemical scurvy.

The normal range for the cholesterol content of the plasma for the method used is 100 to 230 mg per hundred cubic centimeters.

#### RESULTS

The results of the chemical and physical examinations are given in the table.

*Carotene*—Twenty-eight per cent (32) of the 114 diabetic children in this series showed a carotene content of the plasma above the normal, and 17 per cent (19 children), a content below the normal. In the subgroups, the same carotene pattern was evident throughout, with noteworthy deviations from it of an increased and a decreased carotene content of the blood.

*Hypercarotenemia* Forty per cent of the diabetic children exhibiting hepatomegaly, 40 per cent of those with associated cholesteremia and 60 per cent of those with a positive reaction to the tourniquet test (the number of children, 5, with a positive reaction to this test was too small to make possible any valid conclusions concerning this group, and data for them will be omitted in the further discussion of plasma carotene) showed an increase of carotene in the plasma.

*Hypocarotenemia* Ten per cent of the diabetic children with a history of glycosuria and frequent or recent acidosis, 10 per cent of the children with hepatomegaly, none of the children with signs of vitamin A deficiency and 3 per cent of the children with cholesteremia showed a reduction in the carotene content of the blood. None of the subjects had infections, which Clausen and McCoord<sup>6</sup> found to be a cause of hypocarotenemia.

In previous reports, as a rule, the carotene level of the blood has been stated to be elevated. Two other investigators have reported on series of 100 or more cases of diabetes, that is, a number comparable to ours. Rabinowitch<sup>7</sup> demonstrated an excess of carotene in the blood in 426 of 500 cases of diabetes, that is in 85.2 per cent, and Boeck and Yater,<sup>8</sup> in 86 per cent of 100 cases.

6 Clausen, S. W., and McCoord, A. B. Carotinoids and Vitamin A of Blood, *J. Pediatr.* **13**: 635-650 (Nov.) 1938.

7 Rabinowitch, I. M. Carotinemia and Diabetes Relationship Between Sugar, Cholesterol and Carotene Contents of Blood Plasma, *Arch. Int. Med.* **45**: 586-592 (April) 1930.

In the present series only 32 (28 per cent) of 114 diabetic children showed high carotene levels of the blood. More recent contributions have given evidence of lower values for carotene, which are not so consistently above the normal as those cited in earlier analyses. In this connection, the statement of Gordon and Sevringhaus<sup>9</sup> may be quoted: "There is no characteristic pattern in the carotene-vitamin A relationship," a statement which implies (personal communication) that they found a considerable scattering of high and low carotene values among the diabetic patients whom they studied. Thus it appears that as the management of diabetes has progressed, the frequency of hypercarotenemia among patients with diabetes has become less. We believe this can be explained on the basis of better utilization and digestion of fat and a lower incidence of hyperlipemia than existed a decade ago.

From our results (table) it is evident that among diabetic patients exhibiting hepatomegaly, that is, those presumably with fatty infiltration of the liver, or an excess of cholesterol in the blood, the occurrence of hypercarotenemia was much more common and that of hypocarotenemia less frequent than among the diabetic children as a whole. This indicates that when there is a disturbance in the fat metabolism in diabetes, carotene is likely to accumulate in the blood. The small number of cases of hypocarotenemia among the diabetic patients with a history of glycosuria and frequent or recent acidosis bears out the idea that with the accumulation of lipid substances associated with diabetes a mobilization of carotene in the blood occurs.

The cause of hypercarotenemia in diabetes was postulated by Ralli and associates<sup>10</sup> as being an impairment of the function of the liver to convert carotene into vitamin A and the consequent accumulation of carotene within the body. Moore<sup>11</sup> concluded:

The observation of high vitamin A reserves in the livers of subjects dying from diabetes must rule out the suggestion that there is any serious impairment of the power of the liver to convert carotene into vitamin A.

8 Boeck, W. C., and Yater, W. M. Xanthemia and Xanthosis (Carotinemia). Clinical Study, *J. Lab. & Clin. Med.* **14**: 1129-1143 (Sept.) 1929.

9 Gordon, E. S., and Sevringhaus, E. L. Vitamin Therapy and General Practice, ed. 2, Chicago, Year Book Publishers, Inc., 1942.

10 Ralli, E. P., Pariente, A. C., Brandaleone, H., and Davidson, S. Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus. Effect of Daily Administration of Carotene on Blood Carotene of Normal and Diabetic Individuals, *J. A. M. A.* **106**: 1975-1978 (June 6) 1936.

11 Moore, T. Vitamin A and Carotene. Vitamin A Reserve of Adult Human Being in Health and Disease, *Biochem. J.* **31**: 155-164 (Jan.) 1937.

*Data on Status with Respect to Vitamins' A, B and C in Diabetic Children*

Subjects	Type of Data	Plasma Carotene, Micrograms per 100 Ce	Plasma Vitamin A, Micrograms per 100 Ce	Plasma Vitamin A- Carotene Ratio	Plasma Vitamin C, Mg per 100 Ce	Plasma Cholesterol, Mg per 100 Ce
Normal (11)	Mean	195	50	0.26		
	Range	272-139	71-40	0.28-0.21	2.0-0.8*	230-100*
	Standard deviation	±39	±10	0.07		
Diabetic (114)	Mean	231	36	0.18	0.87	204
	Range	420-62	57-16	0.56-0.06	1.74-0.21	454-90
	Standard deviation	±78	±8	0.09	±0.29	±59
	Per cent abnormal	28% above 275 17% below 140	None above 71 68% below 40	11% above 0.28 67% below 0.20	39% between 0.8 and 0.4 4% below 0.4	26% above 230 2% below 100
History of good con- trol of diabetes (58)	Mean	226	35	0.19	0.91	219
	Range	420-62	57-20	0.56-0.06	1.74-0.21	454-90
	Standard deviation	±85	±8	0.11	±0.29	±36
	Per cent abnormal	31% above 275 19% below 140	None above 71 69% below 40	21% above 0.28 64% below 0.20	40% between 0.8 and 0.4 3% below 0.4	24% above 230 0.2% below 100
History of persis- tent glycosuria (35)	Mean	233	36	0.16	0.82	202
	Range	406-98	55-16	0.30-0.08	1.71-0.22	335-93
	Standard deviation	±80	±8	0.05	±0.29	±48
	Per cent abnormal	26% above 275 14% below 140	None above 71 74% below 40	3% above 0.28 74% below 0.20	28% between 0.8 and 0.4 9% below 0.4	20% above 230 0.3% below 100
History of glyco- suria and frequent or recent acidosis (21)	Mean	235	38	0.17	0.80	216
	Range	381-130	53-20	0.34-0.07	1.21-0.22	430-125
	Standard deviation	±74	±10	0.07	±0.22	±76
	Per cent abnormal	24% above 275 10% below 140	None above 71 57% below 40	9% above 0.28 57% below 0.20	57% between 0.8 and 0.4 5% below 0.4	43% above 230 None below 100
Diabetes of more than average (4.3 yr) duration (44)	Mean	211	35	0.20	0.63	213
	Range	406-62	53-19	0.56-0.06	1.74-0.22	309-125
	Standard deviation	±82	±8	0.10	±0.37	±42
	Per cent abnormal	23% above 275 27% below 140	None above 71 70% below 40	16% above 0.28 61% below 0.20	40% between 0.8 and 0.4 2% below 0.4	23% above 230 None below 100
Treated with un- modified insulin (11)	Mean	230	36	0.17	0.84	213
	Range	329-98	55-22	0.34-0.08	1.21-0.22	265-170
	Standard deviation	±75	±7	0.06	±0.28	±26
	Per cent abnormal	36% above 275 18% below 140	None above 71 72% below 40	9% above 0.28 72% below 0.20	36% between 0.8 and 0.4 9% below 0.4	27% above 230 None below 100
Treated with pro- tamine zinc insulin (103)	Mean	231	36	0.18	0.87	203
	Range	420-62	57-16	0.56-0.06	1.74-0.21	454-90
	Standard deviation	±79	±8	0.09	±0.29	±62
	Per cent abnormal	27% above 275 16% below 140	None above 71 68% below 40	12% above 0.28 66% below 0.20	39% between 0.8 and 0.4 4% below 0.4	26% above 230 2% below 100
Signs of vitamin A deficiency (10)	Mean	238	33	0.15	0.85	222
	Range	360-178	53-24	0.30-0.08	1.24-0.46	268-167
	Standard deviation	±64	±8	0.09	±0.21	±37
	Per cent abnormal	30% above 275 None below 140	None above 71 90% below 40	10% above 0.28 80% below 0.20	50% between 0.8 and 0.4 None below 0.4	50% above 230 None below 100
Signs of vitamin B <sub>1</sub> deficiency (20)	Mean	251	38	0.17	0.87	220
	Range	406-75	53-25	0.40-0.08	1.38-0.22	430-143
	Standard deviation	±92	±7	0.08	±0.34	±67
	Per cent abnormal	40% above 275 15% below 140	None above 71 60% below 40	5% above 0.28 65% below 0.20	30% between 0.8 and 0.4 10% below 0.4	35% above 230 None below 100
Signs of riboflavin deficiency (5)	Mean	218	38	0.17	0.87	249
	Range	295-177	51-27	0.26-0.14	1.25-0.68	297-200
	Standard deviation	±44	±8	0.04	±0.21	±33
	Per cent abnormal	20% above 275 None below 140	None above 71 60% below 40	None above 0.28 80% below 0.20	60% between 0.8 and 0.4 None below 0.4	60% above 230 None below 100
Positive tourniquet test (5)	Mean	274	34	0.13	0.94	215
	Range	360-130	55-23	0.17-0.09	1.74-0.46	268-145
	Standard deviation	±79	±11	0.08	±0.44	±51
	Per cent abnormal	60% above 275 20% below 140	None above 71 80% below 40	None above 0.28 100% below 0.20	40% between 0.8 and 0.4 None below 0.4	20% above 230 None below 100
More than 4 inches (10 cm) under nor- mal height (10)	Mean	230	37	0.22	0.97	190
	Range	327-98	53-19	0.66-0.08	1.74-0.46	309-134
	Standard deviation	±91	±10	0.05	±0.34	±48
	Per cent abnormal	30% above 275 20% below 140	None above 71 60% below 40	20% above 0.28 50% below 0.20	30% between 0.8 and 0.4 None below 0.4	10% above 230 None below 100
Hepatomegaly (20)	Mean	245	35	0.17	0.94	203
	Range	394-62	51-22	0.47-0.07	1.38-0.58	309-130
	Standard deviation	±90	±8	0.07	±0.24	±52
	Per cent abnormal	40% above 275 10% below 140	None above 71 65% below 40	5% above 0.28 65% below 0.20	40% between 0.8 and 0.4 None below 0.4	30% above 230 None below 100
Elevated cholesterol level of plasma (30)	Mean	262	39	0.16	0.79	278
	Range	381-98	52-25	0.35-0.08	1.46-0.22	454-230
	Standard deviation	±76	±6	0.06	±0.27	±52
	Per cent abnormal	40% above 275 3% below 140	None above 71 53% below 40	7% above 0.28 76% below 0.20	46% between 0.8 and 0.4 7% below 0.4	100% above 230 None below 100

\* Values accepted in the literature



Murrill and associates<sup>12</sup> observed that carotene administered orally did not increase the vitamin A content of the blood either in normal or in diabetic subjects. From this observation, together with the fact that the entire group of diabetic patients whom they studied had normal vitamin A values in the blood, they decided that there was no indication that the liver of the diabetic patient converts carotene to vitamin A more slowly than that of the normal person.

The idea that a disturbance of fat metabolism is one of the factors responsible for the accumulation of carotene in the blood of diabetic persons has gradually been gaining ground. The solubility of carotene in fat, the direct ratio of the quantity of carotene taken up through the wall of the intestine to the amount of fat absorbed (Ahmad<sup>13</sup>), the high fat diet of diabetic patients and the tendency to hyperlipemia in such persons, all point to the assumption that where there is an excess of fat there will be an excess of carotene, whether this concerns the process of absorption from the intestine, storage in the liver or accumulation in the blood.

Arguments, both pro and con, concerning the direct relation of hyperlipemia and a high fat diet to carotenemia have been put forward. Rabinowitch<sup>7</sup> observed that pronounced hypercarotenemia was associated with severe diabetes, poor prognosis and hypercholesteremia. (All these conditions favor the presence of hyperlipemia.) On the other hand, Boeck and Yater<sup>8</sup> expressed the opinion that the severity of the diabetes, the character of the diet and the fat content of the blood had no bearing on the occurrence of xanthemia, though xanthosis was found more often in cases of severe diabetes, these statements almost in contrary to Rabinowitch's experience. Heymann<sup>14</sup> showed that utilization of carotene was interfered with in diabetes, a disturbance which, in his opinion, was associated not with hypercholesteremia or hyperglycemia but with some other metabolic disturbance. Ahmad<sup>13</sup> demonstrated that the absorption of carotene was largely influenced by the amount of fat in the diet. Murrill and associates<sup>12</sup> expressed the opinion that high values for carotene in the blood in cases of diabetes could be explained by the presence of a high fat content of the blood in these cases. Josephs<sup>15</sup> demonstrated a direct relation of vita-

min A, carotene and the total lipids of the blood. In his experience, the cholesterol parallels the degree of hyperlipemia. He found that diabetic patients without hyperlipemia showed no excess of carotene in the blood. Opinion apparently is divided as to the relation of the absorption and retention of fat and the degree of carotenemia, but the trend of investigation is toward the conclusion that the solubility of carotene in fat aids in the absorption of carotene and determines the extent to which it is present in the blood. In the presence of diabetes, which is often associated with hyperlipemia, a high carotene content may frequently be expected.

Our results—the direct correlation of the carotene level with the degree of cholesteremia and the parallelism between hepatomegaly and hypercarotenemia—support the concept of the dependence of an increase in carotene on its solubility in fat. The more efficient and widespread use of insulin has doubtless resulted in a diminishing incidence of hyperlipemia among diabetic patients, an effect accounting for the less frequent occurrence of hypercarotenemia now than a few years ago. This relation will not be completely understood until further concomitant studies of the lipid and carotene contents of the blood in diabetic subjects are carried out.

*Vitamin A*—In no instance was the vitamin A content of the plasma above the normal. More than half the 114 diabetic children studied (68 per cent, or 78) showed a subnormal level of vitamin A in the plasma. As none of the subjects had infections (which Clausen and McCoord<sup>6</sup> stated resulted in lowering of vitamin A), this factor may be eliminated as a cause of the low values for vitamin A. The occurrence of low vitamin A levels of the plasma in a large proportion of children in whom clinical evidence of lack of vitamin A was elicited (10 subjects) bears out the validity of the accepted signs of avitaminosis A. The only other variation of note in the subgroups concerned the subjects with a positive reaction to the tourniquet test, a very large number of whom (80 per cent) had low values for the vitamin A in the plasma. As mentioned in the discussion of carotene levels of the plasma, the number of patients, 5, with a positive reaction to the tourniquet test is too small to justify any final conclusions regarding the relation of plasma carotene or vitamin A to a positive reaction to the tourniquet test.

The notable depression of the vitamin A content of the plasma in the presence of a tendency to hypercarotenemia in these juvenile diabetic

12 Murrill, W. A., Horton, P. B., Leiberman, E., and Newburgh, L. H. Vitamin A and Carotene Metabolism in Diabetics and Normals, *J. Clin. Investigation* **20** 395-400 (July) 1941.

13 Ahmad, B. Fate of Carotene After Absorption in the Animal Organism, *Biochem. J.* **25** 1195-1204, 1931.

14 Heymann, W. Carotenemia in Diabetes, *J. A. M. A.* **106** 2050-2052 (June 13) 1936.

15 Josephs, H. W. Relation of Vitamin A and Carotene to Serum Lipids, *Bull. Johns Hopkins Hosp.* **65** 112-124 (July) 1939.



patients bears out the observation of Ralli and associates<sup>10</sup> that lowering of vitamin A is due to slowing of the function of the liver in converting carotene to vitamin A. This statement appears to be contradictory to the conclusions reached in discussion of the results of determination of the plasma carotene. However, from our observation of hypercarotenemia in 28 per cent of these juvenile diabetic patients and of depressed vitamin A levels in 68 per cent (with no excess of vitamin A in the plasma in a single instance), there seems to be evidence of some hindrance in the process of conversion of carotene to vitamin A, though this does not in any way invalidate the hypothesis previously formulated that hypercarotenemia accompanying diabetes depends on the presence of an excess of fat in the blood and in the tissues, which is characteristic of unsatisfactorily controlled diabetes. It may be that fat holds the carotene in solution and prevents its being available for conversion to vitamin A by the liver, an assumption explaining both the tendency to high carotene and low vitamin A levels in the plasma in the present determinations.

*Vitamin A-Carotene Ratio*—A large proportion of the vitamin A-carotene ratios for the 114 diabetic children did not fall into the normal range of 0.28 to 0.20. For 67 per cent (76 patients) the ratios were at a level lower than 0.20, which bears out the observations already noted of a high carotene and a low vitamin A level of the plasma and justifies the conclusion previously made that there is some interference in the normal process of conversion of carotene to vitamin A. A ratio above 0.28 in this series was always due to a low carotene level, as is obvious from the fact that none of the vitamin A concentrations were above the normal range. A low carotene intake or a poor absorption of carotene might account for this. On the other hand, the normal or high plasma vitamin A-carotene ratios indicate that utilization of carotene for the formation of vitamin A was normal, or exceeded the normal, in 33 per cent (38) of the patients.

*Vitamin B Complex*—Twenty-three patients, or 20 per cent, had signs of vitamin B deficiency. Of these patients, 18 had vitamin B<sub>1</sub> deficiency alone, 2 had deficiency in thiamine and riboflavin, and 3 had ariboflavinosis alone. Of the 10 subjects with clinical vitamin A deficiency, 4 also had deficiency in one of the vitamin B components. Eight (35 per cent) of the vitamin B-deficient group had hepatomegaly, whereas only 12 (13 per cent) of those without vitamin B deficiency had hepatomegaly. Of the vitamin B-deficient group, 27 per cent had histories of uniformly good control of the diabetes, 43 per cent had histories of persistent glycosuria, and 30 per

cent had had poorly controlled diabetes, with frequent or recent acidosis. All but 1 of these patients were under treatment with protamine zinc insulin.

The plasma studies of the patients with avitaminosis B revealed carotene and vitamin A levels consistent with the values for the entire group of diabetic patients, a slightly higher percentage of these patients had vitamin C levels below the critical point.

Three subjects with cheilosis on arrival at the camp were observed to have healing or healed lesions after the two week period of dietary supervision and better control of their glycosuria. It was of interest to note that 2 of these children stated that they had noticed "sore corners of the mouth" whenever they overindulged in proscribed foods and that the soreness disappeared when they "behaved."

In the study conducted at the camp in 1941,<sup>1</sup> 24 per cent of the children were found to have vitamin B deficiency. In our experience during two successive summers, 20 to 25 per cent of young diabetic patients proved to have vitamin B deficiency. This figure is somewhat higher than that obtained in other investigations.

*Vitamin C*—There were no patients with clinical scurvy, although 5 had positive reactions to tourniquet tests. Four per cent (5 subjects) had a vitamin C level of the plasma below 0.4 mg per hundred cubic centimeters, that is, the level at which chemical scurvy occurs. None of the children with a positive reaction to the tourniquet test showed plasma values below the critical level. This casts doubt on the validity of the Rumpel-Leede test as a criterion of pronounced vitamin C deficiency. Thirty-nine per cent (43) of the entire 114 diabetic children had vitamin C values for the plasma of 0.8 to 0.4 mg per hundred cubic centimeters, a level pointing to tissue unsaturation. Our results, showing few instances of vitamin C deficiency, confirm those of other recent studies<sup>16</sup> on this point. It may be concluded that most diabetic children obtain sufficient vitamin C and have adequate utilization of this vitamin.

*Relation of Control of Diabetes to Vitamin Status*—There was in our opinion no significant difference in the vitamin A or the vitamin C content of the plasma between the children with consistently satisfactory regulation of their diabetes and those with persistent glycosuria or a history of recurring acidosis. Glycosuria without acidosis and without hypercholesteremia appar-

16 Owens, L. B., Wright, J., and Brown, E. Vitamin C Survey in Diabetes, *New England J. Med.* **224**: 319-323 (Feb 20) 1941. Sebesta, V., Smith, R. M., Fernald, A. T., and Marble, A. Vitamin C Status of Diabetic Patients, *ibid.* **220**: 56-60 (Jan 12) 1939.

ently did not cause the carotene level of the plasma to vary remarkably from that for the group as a whole. Among the subjects with recurring acidosis, hypercholesteremia and hepatomegaly a distinct tendency to fewer instances of subnormal levels of carotene in the plasma was apparent, the patients with hepatomegaly, as well as those with hypercholesteremia, included a great number with high values for carotene in the plasma. The possible explanation of this fact has been discussed in the section devoted to carotene. Of the vitamin B-deficient group, 27 per cent had histories of uniformly good control of the diabetes, 43 per cent had histories of persistent glycosuria, and 30 per cent had had poor control of the diabetes, with frequent or recent acidosis. All but 1 of these patients were being treated with protamine zinc insulin. The majority of physicians allow their diabetic patients to exhibit some glycosuria while they are under the influence of protamine zinc insulin, a few countenance a continued high degree of glycosuria. The present observations indicate that avitaminosis B does result when there is persistent glycosuria, even though the diabetic patient is under the influence of protamine zinc insulin.

#### SUMMARY AND CONCLUSIONS

The results of a study made during the summer of 1942 of the status of vitamins A, B and C in 114 diabetic children at the camp conducted by the New York Diabetes Association were as follows:

Plasma carotene	Percentage	No of Patients
Hypercarotenemia	28	32
Hypocarotenemia	17	19
Normal	55	63
Plasma vitamin A		
Above normal	0	0
Below normal	68	78
Normal	32	36
Signs of vitamin A deficiency	9	10
Plasma vitamin C		
Tissue saturation (above 0.8 mg per 100 cc)	57	65
Tissue unsaturation (between 0.8 and 0.4 mg per 100 cc)	39	44
Chemical scurvy (less than 0.4 mg per 100 cc)	4	5
Positive reaction to tourniquet test	4	5
Signs of the thiamine deficiency	18	20
Signs of riboflavin deficiency	4	5

Hypercarotenemia was observed in 28 per cent of the children. In two comparable series of a decade ago, the incidence of hypercarotenemia was about 85 per cent. The less frequent occurrence of an excess of carotene in the blood is ascribed to the more effective treatment of diabetes which has been developed during the last ten years.

Our results—the direct correlation of the carotene level with the degree of cholesteremia and the parallelism between hepatomegaly and hypercarotenemia—support the concept of the dependence of an increase in carotene on its solubility in fat. This matter will not be completely explained until further concomitant studies of the lipid and carotene contents of the blood of diabetic patients are carried out.

In no instance was the vitamin A content of the plasma above the normal. Sixty-eight per cent of the diabetic children (78) showed a subnormal level of vitamin A.

The notable depression of the vitamin A content of the plasma, in the face of a tendency to hypercarotenemia in these juvenile diabetic subjects, can be accounted for on the basis of an excess of fat holding the carotene in solution and preventing its being available for conversion to vitamin A by the liver.

A study of these patients and of our preceding series (more than 200 children) reveals that 20 to 25 per cent of young diabetic patients treated in the clinics of New York city have vitamin B deficiency.

Hepatomegaly occurred frequently when a vitamin B deficiency existed.

Poor control of the diabetes, as judged by a history of persistent glycosuria, was often accompanied by vitamin B deficiency, even though the subjects had been under the influence of protamine zinc insulin.

The Rumpel-Leede (tourniquet) test did not prove to be valid as a sign of avitaminosis C.

There were no cases of clinical scurvy. Five patients (4 per cent of the series of 114 children) had a vitamin C level of the plasma of less than 0.4 mg per hundred cubic centimeters, that is, chemical scurvy. Lack of vitamin C is not a problem in diabetes under the management accorded this disease at present.

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EXPERIMENTAL HYPOPROTEINEMIA AND EDEMA  
STUDIES OF INTESTINAL ABSORPTION AND INTESTINAL ROENTGENOLOGIC  
CHARACTERISTICS

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Comprehensive investigations have been made of the relationship between various deficiency states and the gastrointestinal tract which have resulted in the implication of many deficiencies as causes of disturbed gastrointestinal function. Anorexia, vomiting, diarrhea and other gastrointestinal dysfunctions have been noted in deficiency states,<sup>1</sup> and experimental studies have shown that there are changes in the motility of the stomach and intestine.<sup>2</sup>

The influence of protein deficiency on the gastrointestinal tract has specifically been studied. Barden, Ravdin and Frazier<sup>3</sup> and also Mecray, Barden and Ravdin<sup>4</sup> have shown that the empty-

ing time of the stomach of man and of the dog is noticeably prolonged in the presence of a definite hypoproteinemia, the gastric emptying time varying inversely with the level of plasma proteins. These investigators have also stated the belief that hypoproteinemia may produce so striking an effect on the gastrointestinal tract that severe mechanical defects may be suspected. It has also been demonstrated that hypoproteinemia is associated with a pronounced retardation of the passage of a water-barium sulfate meal through the small intestine of the dog.<sup>5</sup> This decreased motility was accompanied by anatomic changes manifested by bizarre and abnormal roentgenographic patterns of the small intestine. The changes found in hypoproteinemia have been attributed to the edema of the small intestine.

Although these observations may suggest an impairment in intestinal absorption in hypoproteinemia and edema, no direct measurements have as yet been reported. This was the main object of the present study.

#### METHODS

Adult female mongrel dogs were used in all the experiments. For several weeks before they were used they were fed a stock diet consisting essentially of corn meal and meat supplemented with cod liver oil, yeast and bone meal. Measurements of intestinal absorption of galactose and aminoacetic acid were carried out on all the dogs before the production of edema, and these measurements were compared with those obtained on the same animal in the hypoproteinemic condition. In this manner each animal served as its own control, a procedure which greatly increased the reliability of the results.

Edema was produced in the dogs by reduction of plasma proteins by repeated plasmapheresis. This method was probably first used by Morawitz,<sup>6</sup> and the technic has been adequately described by Holman, Mahoney and Whipple.<sup>7</sup> The dogs were trained to lie quietly on a

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6 Morawitz, P. Beobachtungen uber den Wiedersatz der Bluteiweisskorper, *Beitr z chem Phys u Path* **7** 153-164, 1905.

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(Footnote continued on next page)

"dog board" while blood was being removed and solutions injected. About 40 per cent of the dog's blood volume was removed from the femoral artery or the jugular and femoral veins. Clotting was prevented by the use of sodium citrate. The blood was immediately centrifuged in 100 cc centrifuge tubes, the plasma drawn off and the cells resuspended in 0.9 per cent solution of sodium chloride. These were then reinjected into one of the veins. When about half of the cells had been returned to the animal, a further 200 cc of blood was removed. The cells of this blood were kept in the refrigerator and returned to the animal on the next day. This procedure was repeated daily until the plasma proteins were depleted to a suitable level (2 to 3 Gm per hundred cubic centimeters) and a definite edema could be demonstrated. The absorption and motility studies were then repeated.

The plasma which was removed from 2 of the animals was saved, frozen at 20 F and stored at that temperature. After the dogs had been rendered hypoproteinemic and the studies in that state were completed, the plasma was warmed to body temperature and the animals were given reinfusions of all or part of their own plasma. Three or four days after return of the plasma, the dogs appeared to be completely recovered, the plasma protein concentration had returned to normal and all traces of edema had disappeared. At this time the roentgenographic and intestinal absorption studies were repeated. Recovery experiments were not done on the other 3 animals. The time which elapsed from the beginning of the depletion period to the completion of the studies after recovery from the hypoproteinemia was about ten days. During this time the animals were fed a low protein diet, consisting of about 200 Gm daily of a mixture of peeled boiled potatoes and fresh white bread.

Plasma volume and "available (thiocyanate) fluid volume" were determined on 2 of the animals during the control period. These studies were repeated after the dogs had acquired a severe edema and again after the recovery which occurred with plasma transfusion. The methods employed were based on the dilution of the dye T-1824 (plasma volume) and the dilution of thiocyanate (available fluid volume or plasma and interstitial volume) after their intravenous injection. These methods were essentially those described by Gregersen and Stewart<sup>8</sup> as adapted to the use of the Evelyn photoelectric colorimeter.

The methods used to measure the rate of absorption of galactose and aminoacetic acid have already been described in detail.<sup>9</sup> Essentially they depend on the oral administration of the test substance by stomach tube followed by the determination of the concentration of the substance in the blood after definite intervals of time. The type of curve obtained is an indicator of the rate of intestinal absorption. Since the blood concentrations are also affected by the rate of metabolism, this is given consideration in the methods. The metabolism of aminoacetic acid was studied by following the increase in blood urea and urinary excretion of urea. The rate of metabolism of galactose was deter-

by Diet I Liver and Casein as Potent Diet Factors, *J Exper Med* 59:251-267, 1934.

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mined in a separate experiment by the intravenous injection of the sugar over a period of one hour at a constant rate which simulates its rate of entrance into the blood stream from the gastrointestinal tract.

Roentgen studies were carried out on the dogs during the control period after administration by stomach tube of 50 Gm of barium sulfate suspended in 75 cc of water. The passage of the barium meal through the gastrointestinal tract was followed fluoroscopically at frequent intervals, and significant changes were recorded by roentgenograms. The studies were repeated at the time the dogs had edema and again when the dogs had recovered from the edema.

## RESULTS

The control level of plasma protein averaged 5.4 Gm per hundred cubic centimeters, whereas the average level of plasma proteins during the period of edema was 2.6 Gm per hundred cubic centimeters and ranged between 2 and 3.2 Gm. However, at the time many of the tests were being carried out the plasma protein levels of

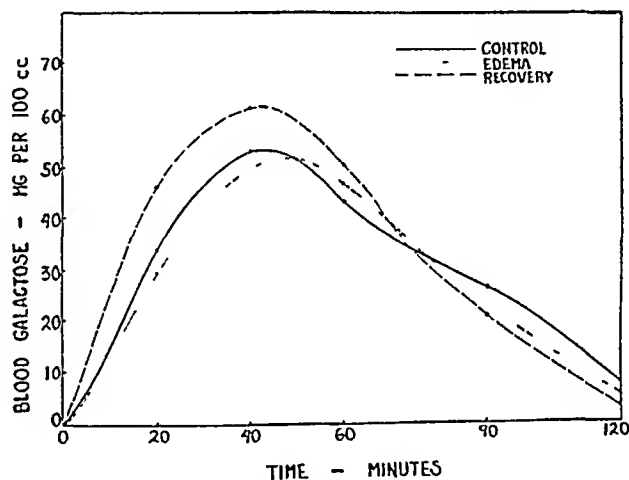


Fig 1—Average blood galactose levels following the oral administration of 0.6 Gm of galactose per kilogram of body weight to dogs before production of edema, during edema and after recovery from edema.

several of the animals were much lower than the values just cited. The average results of studies of galactose absorption are shown in figure 1. It is evident that the blood galactose curves after oral ingestion of the sugar are not significantly different during the time the dogs had edema than during control and recovery periods. The average results of intravenous galactose tolerance studies are shown in figure 2. The curves during control, edema and recovery periods are almost identical in the intravenous studies, indicating that the rates of metabolism are similar. The amounts of galactose excreted in the urine were also similar. In all of the animals there was an insignificant amount of galactose remaining in the stomach one hour after the oral administration of the sugar. This was experimentally ascertained in each of the studies by collection of gastric contents at the end of a one hour period and determination of the galactose content. Since

the rate of metabolism of galactose was not altered by hypoproteinemia, the similarity of the blood galactose curves after oral ingestion is a definite indication that the rate of intestinal absorption was not measurably altered.

The changes in serum amino acid nitrogen and blood urea nitrogen after the oral administration

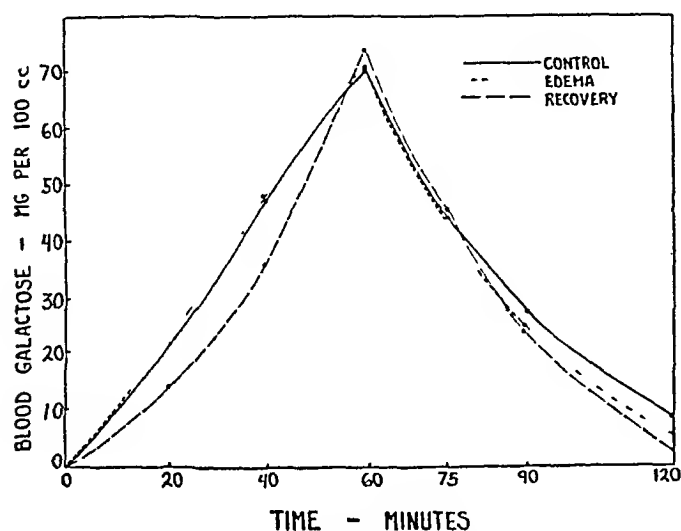


Fig 2—Average blood galactose levels following the intravenous administration of 0.6 Gm of galactose per kilogram of body weight. The sugar was injected at a constant rate during a one hour period. Control values are shown, as well as the curves obtained for the same animals during edema and after recovery.

of aminoacetic acid are shown in figure 3. The average increase in serum amino acid nitrogen was even greater when the dogs were edematous than during the control or recovery period. The increases in blood urea nitrogen were similar during the three periods. The increase in urinary urea nitrogen excretion over the basal level during the six hour period following the oral administration of aminoacetic acid was 100 mg per kilogram per six hours during the control period and 111 mg per kilogram per six hours when the dogs were edematous. The similarity of the changes in the blood urea nitrogen and in the urinary excretion of urea nitrogen indicates no significant change in the rate of aminoacetic acid metabolism. The percentage of administered amino acids converted to urea within six hours was calculated according to the method of Kirk<sup>10</sup>. During the control period the animals on the average converted 60 per cent of the aminoacetic acid to urea. This amount increased to 85 per cent when the dogs were edematous, and during the recovery period it was 53 per cent. As has already been pointed out,<sup>9a</sup> with this dose from 39 to 75 per cent of the aminoacetic acid is usually converted to urea in normal dogs. This is a further indication that the hypoproteinemic dogs are metabolizing the acid in a

manner and at a rate similar to the normal. These results may be interpreted as indicating that the rate of intestinal absorption of aminoacetic acid was not decreased in the presence of edema.

The results of the measurements of plasma volume and available (thiocyanate) fluid volume are given in the table. It can be seen that plasma volumes were not significantly altered by the experimental procedures. The measurements of the available (thiocyanate) fluid volume show a pronounced increase as a result of production of

Plasma and Available (Thiocyanate) Fluid Volumes in Hypoproteinemia and Edema

Dog No	Condition	Weight, Kg	Plasma Volume, Cc	Available (Thiocyanate) Volume, Cc	Plasma Protein, Gm per 100 Cc
89	Control	13.5	600	3900	5.3
	Edema	14.5	615	7200	1.9
	Recovery	11.5	670	3600	5.3
92	Control	14.5	700	4700	4.5
	Edema	17.6	720	7400	2.0
	Recovery	13.0	700	4000	6.0

hypoproteinemia and edema. These figures particularly emphasize that a massive edema was produced in these animals. The available (thiocyanate) fluid volume increased over 20 per cent of the body weight, which was consistent with the edema observed clinically. On restoration of normal plasma protein levels an extensive diuresis occurred, which eliminated the edema and brought the available (thiocyanate) fluid volume back to normal levels.

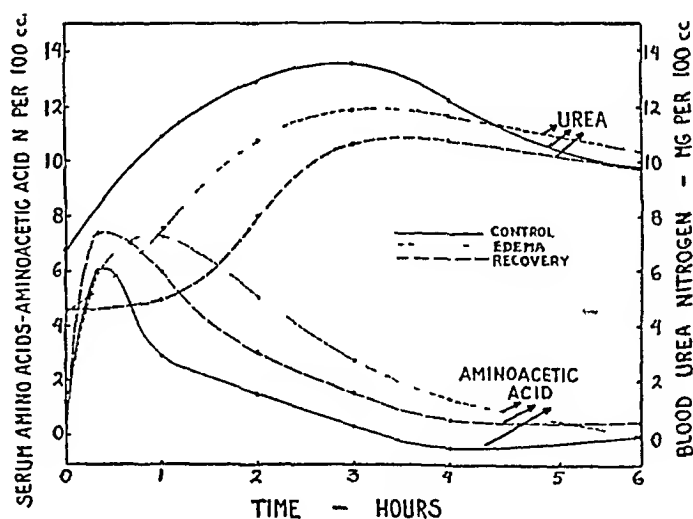


Fig 3—Average increases in serum amino acid nitrogen and changes in blood urea nitrogen following the oral administration of 0.6 Gm of aminoacetic acid per kilogram of body weight. Curves are shown for control dogs, edematous animals and dogs after recovery.

In the 2 animals in which reinfusion of plasma was carried out, the urea excretion during and after the infusion of plasma was studied. A total of 3,050 cc of plasma, containing 81 Gm of protein, was removed from dog 89 during the depletion period. Of this amount, 2,050 cc, con-

<sup>10</sup> Kirk, E. The Ability of Nephritic Patients to Deaminate and Form Urea from Ingested Glycine, *J Clin Investigation* 14:136-141, 1935.

taining 55 Gm of protein, was reinjected intravenously at a constant rate over a twelve hour period. This restored the plasma protein from 2.36 Gm per hundred cubic centimeters to the original normal level, of 5.3 Gm per hundred cubic centimeters. The amount of plasma removed from dog 92 totaled 2,500 cc and contained 71 Gm of protein. This was all returned to the animal over a twenty hour period and elevated the plasma protein from 1.97 Gm to 6 Gm per hundred cubic centimeters, the latter value being even higher than the original control level of plasma protein. The excretion of urea was de-

edematous animals as compared with their control roentgenographic studies. In some of the roentgenograms of the small intestines during edema there was clumping of the barium and segmentation. The significance of this observation is questionable, since these abnormal patterns were noted in some of the roentgenograms obtained from the control group. Whenever clumping and segmentation was noted, it was of a moderate nature. In figure 4 are shown roentgenograms of 2 control dogs and 2 dogs with edema and hypoproteinemia. Figure 4A shows a normal intestinal pattern obtained in a normal control

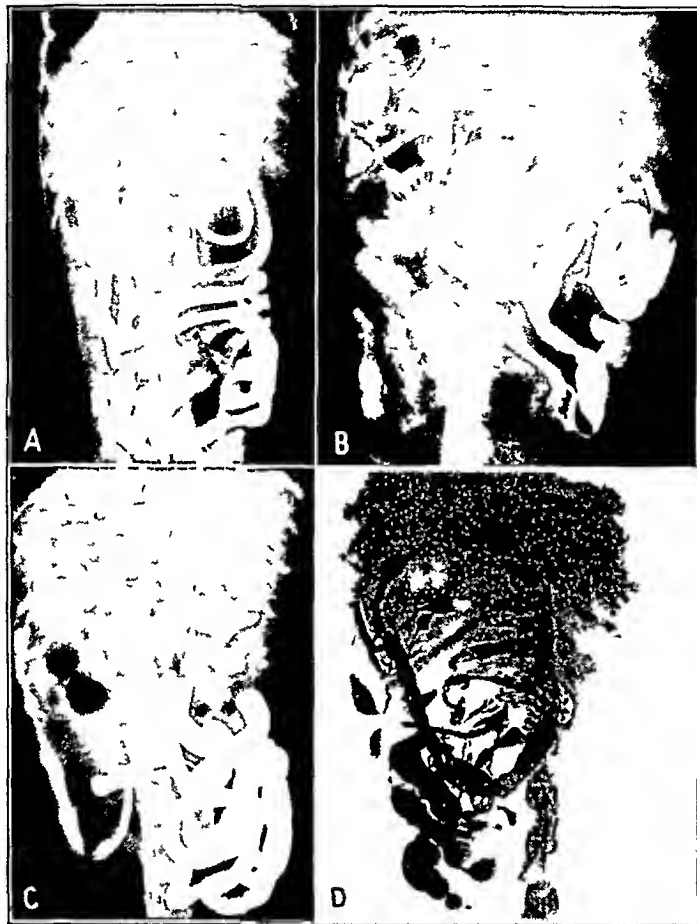


Fig 4—A, dog during control period (plasma protein level 5.3 Gm per hundred cubic centimeters). No changes noted in intestinal pattern. Roentgenogram taken three hours after oral ingestion of aqueous suspension of barium sulfate. B, dog during control period (plasma protein level 5.6 Gm per hundred cubic centimeters). Clumping and segmentation shown. Roentgenogram taken three hours after ingestion of barium sulfate. C, dog during edema (plasma protein level 1.6 Gm per hundred cubic centimeters). No changes noted in intestinal pattern. Roentgenogram taken thirty minutes after ingestion of barium sulfate. D, dog during edema (plasma protein level 1.9 Gm per hundred cubic centimeters). Clumping and segmentation shown. Taken thirty minutes after ingestion of barium sulfate.

termined for the dogs before and after the injections of plasma. The increase in urea excretion was not striking and indicated that most of the plasma protein that was injected was retained, less than 15 per cent of the administered protein being converted to urea during the first forty-eight hours, at which time the rate of urea excretion had returned to the original basal level.

There were no striking differences in the appearances of the intestinal pattern of the

animal, while figure 4B shows clumping and segmentation in a normal control animal. Figure 4C illustrates a normal intestinal pattern obtained in a dog with hypoproteinemia and edema, while figure 4D shows clumping and segmentation in an edematous animal.

Studies of intestinal motility made during the control period were compared with comparable studies on the edematous hypoproteinemic animals. In no instance was the initial emptying



of the stomach delayed during hypoproteinemia. Furthermore, the time required for complete evacuation of the barium meal from the stomach was approximately the same during edema as during the control period or during the recovery period. Observations regarding the speed with which the barium sulfate moved along the intestine indicated that the intestinal motility of the animals was not decreased by hypoproteinemia and edema.

## COMMENT

Since our experiments have shown no changes in gastrointestinal motility or in absorption rates following the production of hypoproteinemia and edema and only slight changes of the intestinal roentgenographic patterns, it should be emphasized that the animals in the present study had lower plasma protein levels and probably more edema than were attained by other investigators who have studied the same phenomena.<sup>11</sup> We have established this fact by numerous observations, which include multiple measurements of plasma protein levels, clinical observations of edema and ascites, gross observations of the visceral edema of 1 of the dogs killed at a time when the plasma proteins were at a low level, pronounced increases in weight and available (thiocyanate) fluid volume, and the production of pronounced diuresis on restoration of the plasma protein concentration to normal values. In the animal which was killed the edema of the visceral organs was even more pronounced than that observed in the skin and extremities. Both the pleural and peritoneal cavities contained considerable free fluid, and all of the abdominal viscera showed clearcut evidences of edema. It should be noted that the critical level of plasma protein concentration at which edema appears in the dog is considerably lower than that at which edema usually appears in human beings with hypoproteinemia.<sup>12</sup> In the present experiments no gross manifestations of edema were noted in any of the dogs as long as the plasma protein concentration was above 3 Gm per hundred cubic centimeters. In the report of Barden, Thompson, Ravdin and Frank<sup>5</sup> no specific mention is made as to whether or not their animals had any demonstrable edema, although they assumed that edema of the intestinal wall accounted for the phenomena noted. From the data presented by these investigators

it would appear that the plasma protein levels of their animals ranged between 3.2 and 4.5 Gm per hundred cubic centimeters.

The roentgenologic methods used for the estimation of gastric emptying time are difficult to evaluate even when employed by skilled operators. In our experiments the presence of hypoproteinemia and edema had little effect on gastric emptying time and on motility of the small intestine. The absence of any decrease in gastric emptying time is adequately confirmed by the normal galactose tolerance curves. We have repeatedly observed by analyses of the gastric residuum that orally administered galactose in doses of 0.6 Gm per kilogram is almost completely emptied in forty-five minutes. The average maximum blood galactose level occurred at forty minutes in both normal and hypoproteinemic states. This offers good evidence to substantiate the occurrence of normal gastric emptying during hypoproteinemia and edema. The roentgen studies on the dogs also indicated that gastric emptying time and intestinal motility were not decreased during edema. These results are not in agreement with those of Barden, Thompson, Ravdin and Frank,<sup>5</sup> who found striking increases in gastric emptying time and decreases in small intestinal motility in dogs kept on a low protein diet for prolonged periods of time. There may have been several factors which could account for the discrepancies. The most evident difference in the two studies is that whereas edema was rapidly produced in our experiments with a minimum change in the condition of the animals other than the lowered plasma protein level, in the experiments of Barden and associates the hypoproteinemia was produced by dietary means. The diet and nutritional condition of the animals may have accounted for the changes in gastrointestinal motility to which hypoproteinemia per se may have contributed only an insignificant amount.

In sprue there is a pronounced impairment in intestinal absorption and there is also a significant change in the intestinal roentgen pattern.<sup>13</sup> This may suggest that there is a correlation between impaired intestinal absorption and abnormal roentgenographic observations, and many authors have spoken of this possibility. In certain conditions other than sprue evidence of impaired

11 McCray, Barden and Ravdin.<sup>4</sup> Barden, Thompson, Ravdin and Frank.<sup>5</sup>

12 Leiter, L. Experimental Edema, *Proc Soc Exper Biol & Med* **26** 173-175, 1928. Moore, N. S., and Van Slyke, D. D. The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J Clin Investigation* **8** 337-355, 1930.

13 Mackie, T. T. Non-Tropical Sprue, *M Clin North America* **17** 165-184, 1933. Snell, A. M. Tropical and Non-Tropical Sprue (Chronic Idiopathic Steatorrhea). Their Probable Interrelationship, *Ann Int Med* **12** 1632-1671, 1939. Kantor, J. L. The Roentgen Diagnosis of Idiopathic Steatorrhea and Allied Conditions, *Am J Roentgenol* **41** 758-778, 1939. Sussman, M. L., and Wachtel, E. Factors Concerned in the Abnormal Distribution of Barium in the Small Bowel, *Radiology* **40** 128-138, 1943.

absorption and abnormal roentgen patterns are obtained simultaneously.<sup>14</sup> In the case of clinical hypoproteinemia and edema most current opinion seems to favor the idea that there is an abnormal roentgen pattern in the intestine, although there have been no extensive clinical reports published on this subject. This is hard to understand, since there is a great abundance of clinical material available and it has been seven years since Pendergrass and associates<sup>15</sup> called attention to this possibility as a result of observations on 1 subject. From a clinical standpoint there is no evidence to suggest that in edema there is a significant impairment in intestinal absorption as evidenced by large amounts of fat and nitrogen in the stool. The present studies demonstrate experimentally that intestinal absorption is not appreciably affected by hypoproteinemia and edema.

The plasma volume in edema has been studied by many different technics with rather discordant results. Harris and Gibson<sup>16</sup> have reviewed the results of many of these studies and have reported plasma volume values in a series of patients with edema, the plasma volume being determined by the injection of the dye T-1824. These investigators noted that in edema the average plasma volume is slightly increased above the normal average. The present observations indicate that in edema due to hypoproteinemia there is no significant change in plasma volume as measured by the dilution of the dye T-1824 but that there is a great increase in interstitial fluid volume as measured by the dilution of intravenously injected thiocyanate.

The results of the nitrogen balance studies carried out after restoration of plasma protein are in agreement with the observations of Elman and Davey,<sup>17</sup> who noted that there is a tenacious

retention of protein nitrogen when administered intravenously to hypoproteinemic subjects.

Recent observations have indicated that impaired hepatic function may be associated with nutritional hypoproteinemia in dogs<sup>18</sup> and hypoproteinemia due to nephrosis in children.<sup>19</sup> The evidence for impaired hepatic function was obtained by retention of plasma amino acid following injection of casein hydrolysate. In our experiments, although there appeared to be a small retention of plasma amino acids following ingestion of aminoacetic acid in the hypoproteinemic dogs, there were no changes in the increase in concentration of urea in the blood or in urinary excretion of urea. The curves after the intravenous administration of galactose were also normal and indicated no impairment of hepatic function in our animals.

#### SUMMARY AND CONCLUSIONS

Hypoproteinemia with edema was produced in 5 dogs by means of plasmapheresis.

The intestinal absorption of galactose and aminoacetic acid was studied by means of improved tolerance tests. The presence of hypoproteinemia and edema had no significant effect on the rate of intestinal absorption of galactose and aminoacetic acid.

Roentgenologic observations of the gastrointestinal tract were made after the oral administration of barium sulfate. Gastric emptying and intestinal motility were not altered by hypoproteinemia and edema. In some of the roentgenograms of the small intestine during edema there was moderate clumping of the barium and segmentation. These phenomena were also noted in the studies on normal animals, although they occurred less frequently.

Studies of plasma volume and available (thiocyanate) fluid volume indicated that during edema the plasma volume is not significantly altered but that the available (thiocyanate) fluid volume is noticeably increased.

The rate of metabolism of galactose and aminoacetic acid was not altered by hypoproteinemia and edema.

The members of the roentgenologic department of University Hospitals cooperated in these studies, and Mrs. Annabelle Miller gave technical assistance.

14 Lepore, M. J., and Golden, R. A Syndrome Due to Deficiency of the Vitamin B Complex, *J. A. M. A.* **117** 918-923 (Sept. 13) 1941. Beams, A. J., Free, A. H., and Glenn, P. M. The Absorption of Galactose from the Gastro-Intestinal Tract in Deficiency Diseases, *Am. J. Digest. Dis.* **8** 415-421, 1941.

15 Pendergrass, E. P., Ravdin, I. S., Johnston, C. G., and Hodes, P. J. Studies of the Small Intestine. II. The Effect of Foods and Various Pathologic States on Gastric Emptying and the Small Intestine Pattern, *Radiology* **26** 651-662, 1936.

16 Harris, A. W., and Gibson, J. G. Clinical Studies of the Blood Volume. VII. Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, *J. Clin. Investigation* **18** 527-536, 1939.

17 Elman, R., and Davey, H. W. Studies on Hypoalbuminemia Produced by Protein-Deficient Diets. III. The Correction of Hypoalbuminemia in Dogs by Means of Large Plasma Transfusions, *J. Exper. Med.* **77** 1-6, 1943.

18 Goettsch, E., Lyttle, J. D., Grim, W. M., and Dunbar, P. Amino Acid Studies. I. Plasma Amino Acid Retention in the Hypoproteinemic Dog as Evidence of Impaired Liver Function, *J. Biol. Chem.* **144** 121-134, 1942.

19 Lyttle, J. D., Goettsch, E., Greeley, D. M., Grim, W. M., and Dunbar, P. Amino Acid Studies. II. Plasma Amino Acid Retention as Evidence of Impaired Liver Function, Investigations in Children with Nephrosis and Liver Disease, *J. Clin. Investigation* **22** 169-181, 1943.

# BRONCHOSPASM ASSOCIATED WITH PULMONARY EMBOLISM

## RESPIRATORY FAILURE

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Increasing awareness of the importance of pulmonary embolism is becoming apparent in the thinking of surgeons and internists alike. Many aspects of the problem have been studied in the laboratory and at the bedside, yet there is still much to be learned concerning both the prophylaxis and the management of this important and extremely common complication in medical, surgical and obstetric patients.

The possibility that bronchospasm may be associated with pulmonary embolism, with material increase in respiratory distress and anoxemia, has been suggested by several investigators. In 1920 Dunn<sup>1</sup> described histologic changes in embolized lungs consisting of spasm of the musculature of the bronchiolar terminations and of the atria, but not of the bronchioles themselves. In 1924, however, Binger, Brow and Branch<sup>2</sup> observed similar changes in normal, nonembolized lungs. Singh,<sup>3</sup> using an oncometer to measure changes in the lung volume of decapitated cats, reported that air embolism produced bronchospasm which could not be prevented by atropine, but which could be abolished by epinephrine. His explanation of the reflex mechanisms involved in decapitated animals is cumbersome and inadequate. His deduction that the effects of epinephrine were exerted on the airways, rather than on the pulmonary circulation, are unconvincing in view of the unreliability of the oncometric method when used with organs containing both blood and gases.

Binet and Burstein<sup>4</sup> produced embolization of the lungs of dogs by the intravenous injection of

lycopodium in oil and, employing a modification of Jackson's<sup>5</sup> method for the registration of bronchial reactions, were able to show bronchoconstriction which could be abolished by atropine or by vagotomy. Judging from their published records, which showed a precipitous fall in blood pressure without recovery, one may conclude that the animals had been subjected to rapidly fatal massive embolization. The practical importance of bronchospasm under such conditions is open to question.

Jesser and de Takáts,<sup>6</sup> in an investigation of the roentgenographic pattern of the bronchial tree after injection of chloriodized peanut oil, reported changes in the pattern following pulmonary embolism which they interpreted to mean constriction of the bronchi. They stated that roentgenograms of the normal bronchial tree of the dog showed that only the large bronchial radicles filled with radiopaque material, and that after pulmonary embolism the smaller radicles became filled. It was evidently their opinion that contraction of the large bronchi had forced the contrast medium into the fine radicles. It is probable that if any reflex bronchospasm occurred it would be most evident in the more muscular bronchioles, filling of which would be more, rather than less, difficult. One might, therefore, be justified in interpreting their results as indicating dilation of the small bronchi and bronchioles. They stated the belief that they had eliminated increased respiratory effort as the cause of the change in bronchial pattern by showing that no change appeared in the normal bronchogram when violent respiratory efforts were induced by clamping the trachea. This method did not conclusively demonstrate the point, for it eliminated the distending and displacing force of the intruding air.

Because of certain objections to some of the methods employed, as well as the possible importance of such bronchial reactions if they do occur, it seemed desirable to reexplore the problem.

5 Jackson, D. E. *Experimental Pharmacology and Materia Medica*, ed 2, St. Louis, C. V. Mosby Company, 1939.

6 Jesser, J. H., and de Takats, G. *The Bronchial Factor in Pulmonary Embolism, Surgery* 12:541, 1942.

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From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

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2 Binger, C. A. L., Brow, G. R., and Branch, A. *Experimental Studies on Rapid Breathing. I. Tachypnea, Independent of Anoxemia, Resulting from Multiple Emboli in the Pulmonary Arterioles and Capillaries*, *J. Clin. Investigation* 1:127, 1924-1925.

3 Singh, I. *Certain Effects of Pulmonary Gas Embolism*, *J. Physiol.* 87:11, 1936.

4 Binet, L., and Burstein, M. *Le bronchospasme au cours des embolies pulmonaires*, *Mem. Acad. de chir.* 64:1297, 1938; *Recherches sur la motricité des bronches*, *Presse med.* 47:217, 1939.

## METHODS

Two methods for the recording of bronchial reactions were used in the present study. The first method consisted in rhythmic inflation of the lungs of anesthetized dogs with a force pump which delivered a constant volume of air into the trachea at a constant rate, variations in intratracheal pressure being recorded at the same time. It was assumed that a change in resistance to the flow of air brought about by changes in the caliber of the bronchial tree would be reflected by corresponding changes in intratracheal pressure. In order to eliminate the effects of the animal's own respiratory efforts, which may become violent after embolism, it was necessary to open the chest widely. This was accomplished by splitting the sternum and retracting its edges. The need for deep anesthesia and extensive operative procedures introduces serious objection to the method.

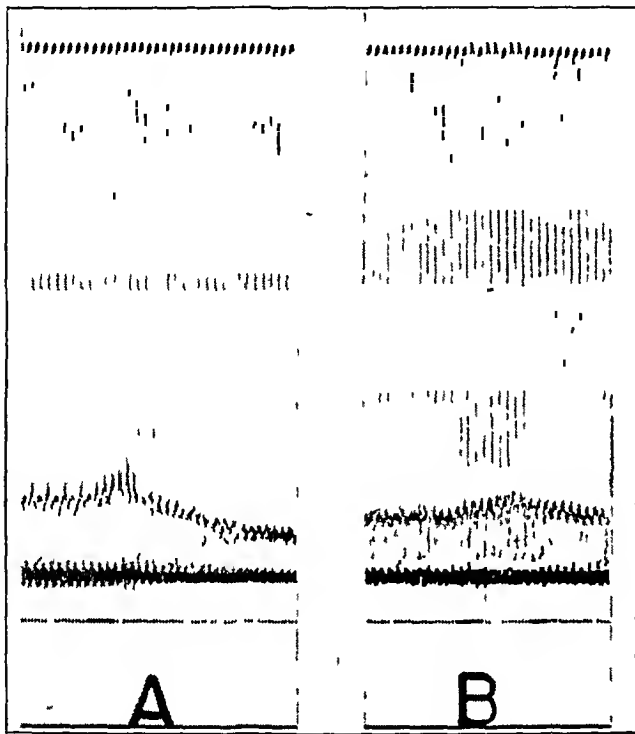


Fig 1—Tests of the validity of one of the methods used to record bronchial reactions. The animal was receiving artificial respiration, the lungs being inflated by a pump which delivered a constant volume of air at a constant rate. Any change in intratracheal pressure (upper curve) indicates a change in the resistance to the flow of air into the lung. *A* shows the effects of intravenous injection of 0.2 mg of histamine phosphate on the intratracheal pressure and the pressure in the right ventricle (lower curve). Downward deflection indicates increased intratracheal pressure. *B* shows the effects of clamping the hilus of one lobe of the lung. The time interval equals one second.

The second method consisted of simultaneous registration of intratracheal and intrapleural pressures in normally breathing, lightly anesthetized dogs. It was assumed that if the intratracheal and the intrapleural pressure changed in opposite directions, a change in the patency of the bronchial tree had occurred. The principle is essentially that involved in Jackson's method except that in the latter the changes in intrapleural pressure are kept constant by means of a rhythmic suction pump. Thus, if intratracheal pressure decreased while intrapleural pressure increased, it was assumed

that bronchoconstriction had occurred. We also accepted as indicating bronchoconstriction records which showed no change in intratracheal pressure despite significant increases in intrapleural pressure. We have been unwilling to accept as evidence of bronchoconstriction records in which both intrapleural and intratracheal pressure increased, even though the increase in the intrapleural pressure was disproportionately greater than the increase in intratracheal pressure. It is possible that such changes are valid evidence of bronchoconstriction, but we have been reluctant to accept them as such.

The results of procedures designed to test the validity of the methods are shown in figures 1 and 2. Figure 1*A* shows the effect of intravenous injection of 0.2 mg of histamine phosphate on the intratracheal pressure (upper curve) and the pressure in the right ventricle (lower curve) in an animal prepared by the first method. The maximum intratracheal pressure which developed during the "inspiratory" phase (downward deflection) was increased definitely but not conspicuously. Indeed, the degree of change was surprisingly small in view of the fact that direct observation of the lungs revealed little, if any, inflation. Figure 1*B* illustrates the effects of clamping the hilus of the upper lobe of the right lung. The increase in intratracheal pressure was again definite but not pronounced.

The tests seemed to indicate that the method was valid for demonstration of high degrees of bronchoconstriction but that it was probably not sensitive to less intense bronchial reactions.

Figure 2 shows the effect of injection of 0.5 mg of acetylbetamethylcholine chloride on intratracheal pressure (upper curve) and intrapleural pressure (lower curve) in the normally breathing animal (method 2). It will be noted that, despite a notable increase in intrapleural pressure, little, or no, variation in pressure occurred in the trachea until the effects of the drug began to wear off. Although this method proved to be more sensitive than method 1, it has certain limitations, the most important of which is the difficulty in evaluation of differential changes in the intratracheal and intrapleural pressures during changes in the respiratory rate and the duration of the respiratory phases. In the evaluation of experimental results this factor must be given due consideration.

## PROCEDURE

Mongrel dogs, weighing 6 to 10 Kg, were anesthetized with sodium pentobarbital (40 mg per kilogram of body weight in experiments with method 1 and 20 to 25 mg per kilogram of body weight in experiments with method 2). When measurements of pressure in the right ventricle were made, the animal's blood was rendered noncoagulable by the use of heparin (1 mg per kilogram of body weight) and calomine fast pink<sup>7</sup> (120 mg per kilogram of body weight).

Large pulmonary emboli were produced by the intravenous injection of a suspension of barium sulfate<sup>8</sup> or by introduction into the venous circulation of thin sheet rubber cut into strips 15 cm long and 15 mm wide. The method of introduction of the rubber strips was as follows. The external jugular vein was cannulated with a glass tube having an inner diameter of 2 mm and sufficient length to allow its passage into the superior vena cava. Rubber emboli were then fitted into a number of similar glass tubes, and the tubes filled with

7 This substance was furnished by Calco Chemical Company, Bound Brook, N. J.

8 de Takats, G., Beck, W. C., and Fenn, G. K. Pulmonary Embolism, Surgery 6:339, 1939.

isotonic solution of sodium chloride. A tube containing an embolus was connected to the cannula by means of rubber tubing and the embolus forced into the vena cava by the injection of isotonic solution of sodium chloride from a syringe. These emboli were soft and pliable, passed readily through the chambers of the heart and, after blocking some of the larger branches of the pulmonary artery, accumulated in the main pulmonary artery to form a rider embolus, as shown in the accompanying sketch (fig 3). This proved to be a simple and effective method for the repeated introduction of

two emboli had no apparent effect on intratracheal pressure, this result indicating that the presence of the foreign bodies in the pulmonary arteries did not produce demonstrable reflex effects on the bronchi, nor was the resistance in the pulmonary circuit sufficiently increased to be reflected in changes in pressure in the right ventricle. A few seconds before the introduction of the fourth embolus the pressure in the right

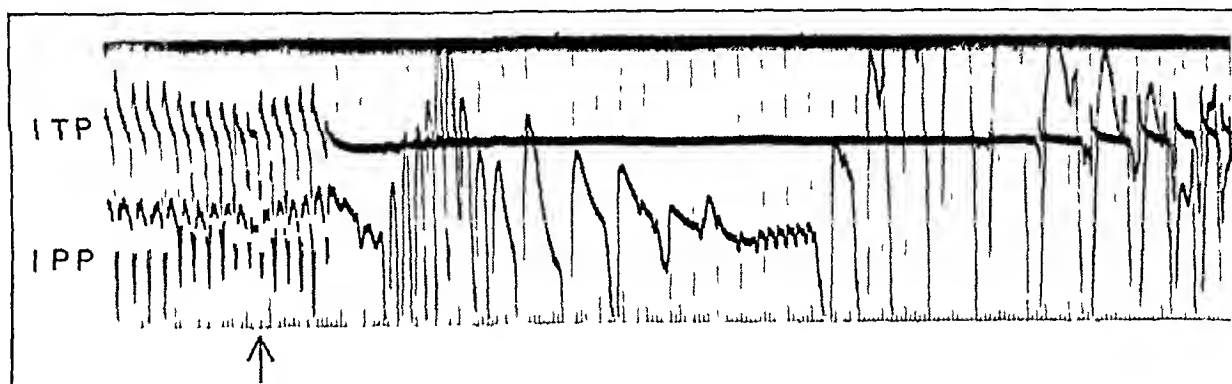


Fig 2—Effects of intravenous injection of 0.5 mg of acetylcholine chloride (mecholyl chloride) on the intratracheal pressure (ITP) and the intrapleural pressure (IPP) in a normally breathing, lightly anesthetized dog. Bronchoconstriction is indicated by a decrease in the intratracheal pressure despite a conspicuous increase in the intrapleural pressure. Time intervals, four-hundredths and two-tenths seconds.

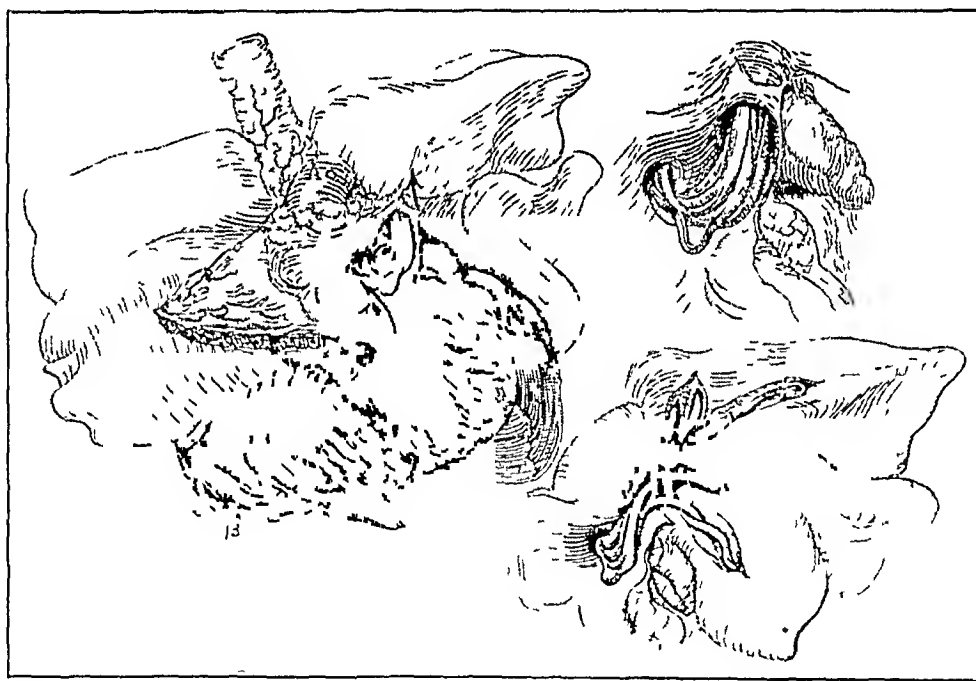


Fig 3—Drawing of the pulmonary arteries filled with rubber emboli. For description see text.

moderate-sized emboli, and, by injection of the rubber strips in rapid succession, massive embolism of the main pulmonary artery was produced. From eight to twelve such emboli were sufficient to block effectively the pulmonary circulation and to cause the death of the animal.

#### RESULTS

*Method 1*—Figure 4 shows the effects of repeated introduction of rubber strips into the pulmonary circulation on the intratracheal pressure (upper curve) and the right ventricle (lower curve). It will be noted that the first

intraventricular pressure gradually rose, and, simultaneously, there was an increase in the maximum intratracheal pressure (downward deflection), a phenomenon which we interpret to indicate bronchoconstriction. It will be noted that the latter effect disappeared toward the end of the recording, even though the intraventricular pressure remained elevated. Although the increase in the recorded amplitude of intratracheal pressure was not striking, it represented almost as great a percentile increase as that produced by

the intense bronchoconstriction induced by histamine, shown in figure 1

In only 3 of 10 experiments with this method were effects produced comparable to those illustrated in figure 4. In 2 other experiments there was suggestive, but unreliable, evidence of slight bronchoconstriction. It was because of the inconsistency of results, together with the evident lack of sensitivity of the method, that we turned to the second method.

**Method 2**—In figure 5 are shown the effects of an embolus consisting of 0.5 cc. of a suspension of barium sulfate on intratracheal pressure (upper curve) and intrapleural pressure (lower curve) in the normally breathing, lightly anes-

#### EFFECT OF DRUGS AND VAGOTOMY

Because bronchoconstriction associated with pulmonary embolism was transient as measured by the methods used, it was necessary to inject a drug or sever the cervical vagus nerves before the introduction of emboli and to evaluate the effectiveness of such procedures in the prevention of bronchoconstriction, rather than in the treatment of constriction after it had occurred.

**Papaverine**—Papaverine has been widely used to combat arterial spasm and has been recommended in the treatment of pulmonary embolism because it was observed to overcome bronchospasm,<sup>6</sup> dilate the pulmonary arterial tree<sup>8</sup> and increase the blood flow in the coronary arteries.<sup>9</sup>

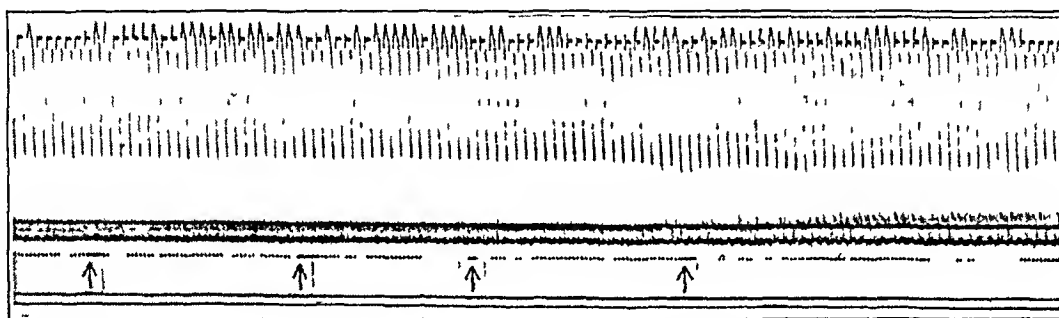


Fig 4—Effects of repeated introduction of rubber emboli on intratracheal pressure and pressure in the right ventricle. The animal was receiving artificial respiration (method 1). The injections of emboli are marked by arrows. For further discussion see text. Time interval, one second.

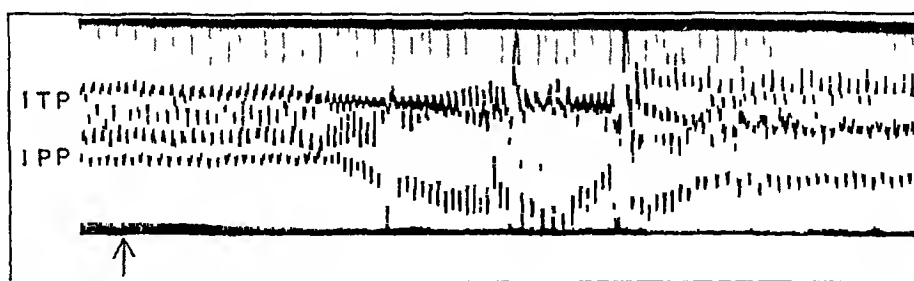


Fig 5—Effects of an embolus of 0.5 cc. of barium sulfate on the intratracheal (ITP) and the intrapleural (IPP) pressure in a normally breathing dog. The decrease in intratracheal pressure despite an increase in pleural pressure is similar to the effect of a known bronchoconstrictor substance, such as that shown in figure 2. Time is expressed in four-hundredths and in two-tenths second.

thetized dog. Despite a notable increase in intrapleural pressure, the intratracheal pressure was temporarily much diminished, although the changes were less than those produced by mecholyl chloride, as illustrated in figure 2. The bronchospasm was apparently transitory, but if we were to accept disproportionate increases in intratracheal and intrapleural pressures as indicative of bronchial reactions, the effect would be somewhat more sustained.

Changes similar to those already described were encountered in 5 of 7 animals with which this method was used. Thus the percentage of positive results was considerably greater with method 2 than with method 1.

Papaverine was observed to quiet the increased respiratory efforts associated with experimental pulmonary embolism following a temporary phase of stimulation of respiration.<sup>10</sup>

We have also observed brief stimulation of respiration, lasting ten to thirty seconds, pro-

9 Essex, H. E., Wegria, R., Herrick, J. F., and Mann, F. C. The Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, *Am Heart J* 19: 554, 1940. Lindner, E., and Katz, L. N. Further Observations on the Action of Drugs on the Caliber of Coronary Vessels, *J Pharmacol & Exper Therap* 72: 306, 1941.

10 Megibow, R. S., Katz, L. N., and Feinstein, M. Kinetics of Respiration in Experimental Pulmonary Embolism, *Arch Int Med* 71: 536 (April) 1943.



duced by papaverine. After this transient stimulation respirations became quieter, and the animal seemed to be somewhat protected against the lethal effects of embolization.

Records of the bronchial reactions, however, proved somewhat surprising, for there regularly appeared evidence of transient bronchoconstriction which was not followed by demonstrable bronchodilation. The temporary increase in resistance to the flow of air into the lungs appeared at the time of, and persisted for as long as, the initial stimulation of respiration. The drug usually produced a fall in pressure in the right ventricle, but in 1 experiment a rise was observed, bronchoconstriction occurred independently of changes in the intraventricular pressure, as shown in figure 6.

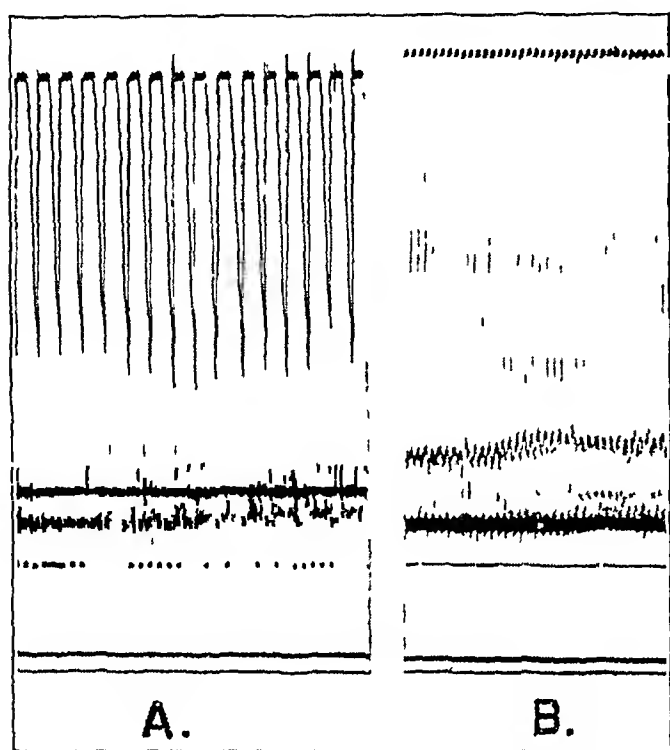


Fig 6—Effects of papaverine on intratracheal pressure and pressure in the ventricle in dogs receiving artificial respiration. There was a brief increase in resistance to the flow of air into the lungs, as indicated by a higher maximal intratracheal pressure (downward deflection). For further discussion see text.

*Atropine and Cervical Vagotomy*—Four animals were subjected to pulmonary embolization after atropinization (1 to 2 mg of atropine sulfate intravenously) or cervical vagotomy. None showed evidence of bronchoconstriction. The number is too small to permit more than the tentative conclusion that the reflex is mediated over the vagus nerve.

*Digitalis*—It has been suggested by Jesser and de Takáts<sup>6</sup> that drugs which increase vagal tone, such as digitalis, increase the degree of bronchoconstriction associated with pulmonary embolism and are therefore contraindicated. We were unable to detect any clear evidence of in-

creased bronchospasm following the intravenous administration of 0.4 mg of lanatoside C<sup>11</sup> in 4 embolized dogs.

#### COMMENT

The transient nature of the bronchoconstriction which appeared after pulmonary embolism raises doubt concerning its practical importance. Further doubt is cast by the observation of Megibow, Katz and Feinstein<sup>10</sup> that in the early stages of experimental pulmonary embolism the oxygen content of arterial blood was increased and the carbon dioxide content decreased. Their observations seem hardly consistent with the production of intense and sustained bronchospasm. It is possible that in unanesthetized human beings bronchoconstriction might be more sustained than in the experimental animal, although we have never encountered clinical evidence in the form of asthmatic breathing in patients with normal hearts. In persons with underlying heart disease, however, pulmonary embolism may precipitate acute heart failure, with cardiac "asthma."

Since atropine has appeared useful, on empiric grounds, in the treatment of pulmonary embolism,<sup>8</sup> and since it may be expected to counteract any bronchospasm which may be present, its use is recommended even though the clinical importance of bronchoconstriction remains in doubt. Epinephrine should not be used for the control of possible bronchospasm associated with pulmonary embolism because of the observation (our own and others<sup>9</sup>) that under such conditions intense pulmonary edema often follows. The demonstration that papaverine appears to produce brief bronchoconstriction should not be a bar to its use, in view of its apparently beneficial effects on other structures.

Megibow, Katz and Feinstein<sup>10</sup> reported evidence that the accelerated respiration following pulmonary embolism was dependent on a rise in pressure in the pulmonary artery, the right chambers of the heart and the superior vena cava. Our observations suggest that the reflex producing bronchospasm may have the same cause, for in experiments in which the pressure in the right ventricle was measured, we did not observe bronchoconstriction in the absence of a rise in pressure in the right ventricle. Disappearance of bronchoconstriction, after an interval of one or two minutes, even though intraventricular pressure remained elevated, suggests—aside from the possibility that some factor other than the rise in pressure provided the stimulus for the reflex—that compensatory or antagonistic mechanisms

<sup>11</sup> This substance was furnished by the Sandoz Chemical Works, Inc., New York.

were set into action or that fatigue and adaptation occurred in the reflex arc

*Respiratory Failure*—So much attention has been given to the heart and circulation in both clinical and experimental pulmonary embolism that it seems desirable to direct attention to the observation that death from pulmonary embolism in the spontaneously breathing experimental animal was generally due to respiratory, and not to cardiac, failure. In most experiments the heart continued to beat regularly for thirty to ninety seconds after respiration had ceased.

While these observations indicate that death was due principally to respiratory failure, it does not necessarily follow that circulatory changes did not play an important role. Respiratory failure is usually to be attributed to depression of the respiratory center by drugs, such as opiates or barbiturates, or to anoxia of the center. Anoxia of the center may be brought about by low oxygen saturation of arterial blood or by a reduction in blood flow. The reduction in blood flow, in turn, may be due to a decrease in systemic arterial pressure or to an increase in venous (or intracranial) pressure or to both. It is evident that under the conditions of our experiments on barbitalized dogs, and, to a large extent, in human beings, all of these factors may be present in varying degrees. In the later stages of pulmonary embolism anoxemia frequently occurs, and at the same time there may be a fall in arterial and a rise in venous pressure. Thus the circulatory effects of pulmonary embolism may be important contributory, or even primary, factors in failure of respiration.

Two types of respiratory failure were seen. The more common one was characterized by periodic breathing of the Cheyne-Stokes form, followed by gradual cessation of breathing, with the usual final slow, gasping efforts. This type of failure followed a prolonged period of rapid, labored breathing, and it is probable that the increased activity of the center hastened its exhaustion. Oxygen therapy not only combats anoxemia, but, by so doing, reduces the respiratory rate,<sup>12</sup> and hence the metabolism of the respiratory center. Thus, not only the oxygen supply to the center is increased, but, at the same time, its oxygen requirement is diminished. Papaverine was the only drug of a number tried by Megibow, Katz and Feinstein<sup>10</sup> that had any significant effect in reducing the accelerated respiratory rate associated with experimental

pulmonary embolism. This drug can, therefore, be considered useful, if only for the purpose of diminishing the metabolic activity of the center. It is probable, however, that its more important action is in removing the underlying causes of the original acceleration. Thus these two agents (oxygen and papaverine) may be expected to stave off exhaustion of the respiratory center. Depression of the center by injudicious use of opiates or barbiturates is of course to be avoided.

The second type of respiratory failure was observed in animals which were subjected to repeated introduction of emboli while they were in respiratory distress from previous embolization. This type of respiratory failure was sudden, and so complete that even the terminal gasping, usually a hardy respiratory function, was completely abolished. The suddenness and completeness of the failure of respiration suggested reflex inhibition of the center, although such an effect is not proved, and equally tenable alternative explanations are available.

The mechanism of sudden death in cases of repeated pulmonary embolism was investigated by Villaret, Justin-Besançon and Bardin.<sup>13</sup> They found that vagotomy, the administration of ephedrine sulfate and atropine together, or alkalinization by the administration of sodium bicarbonate, all acted favorably in delaying death or in increasing the number of emboli tolerated. Conversely, section of the cervical sympathetic nerves or acidification by the injection of hydrochloric acid decreased the animal's tolerance to emboli and hastened the onset of sudden death. They concluded that reflex inhibition of the sympathetic system was responsible for sudden death and that such factors as the  $p_H$  of blood or tissues may be modifying factors. Their experimental results, however, do not exclude alternative mechanisms. For example, vagotomy slows the rate of discharge of the respiratory center in normal animals and, to a less extent, in animals with pulmonary embolism. If the oxygen requirements of the center are thus reduced its eventual deterioration may be postponed. The efficacy of ephedrine may have depended largely on its ability to raise arterial pressure so that blood flow to the center was increased, and hence its oxygen supply improved. Whatever the mechanism of sudden death may be, these experimental results indicate that it can be favorably influenced by drugs.

12 Binger, C. A. L., Brow, G. R., and Branch, A. Experimental Studies on Rapid Breathing. II. Tachypnea, Dependent upon Anoxemia, Resulting from Multiple Emboli in the Larger Branches of the Pulmonary Artery, *J. Clin. Investigation* **1** 155, 1924-1925.

13 Villaret, M., Justin-Besançon, L., and Bardin, P. *Physio-pathologie des accidents mortels consécutifs aux embolies pulmonaires*, Bull. et mem. Soc. méd. d'hop. de Paris **52** 936, 1936, *Recherches sur la prévention expérimentales des accidents consécutifs aux embolies pulmonaires*, *ibid.* **52** 941, 1936.

The treatment of pulmonary embolism resolves itself into maintenance of an adequate oxygen supply to the heart muscle and to the respiratory center. When there is arterial anoxemia, much can be expected from oxygen therapy, but alone it may be insufficient. A pressor drug, such as epinephrine, might be expected to improve the blood supply to the heart and to the medulla, but use of this drug may be unsuitable under the circumstances. Its tendency to produce pulmonary edema has been mentioned. In addition, epinephrine increases general metabolism, increases the work of the heart and produces an increase in venous pressure. Ephedrine, on the other hand, produces a greater and more sustained rise in blood pressure, at the same time, it does not increase the metabolic rate and cardiac work to as great an extent as does epinephrine.<sup>14</sup> There is, therefore, both theoretic and experimental evidence to indicate that ephedrine may be useful in combating respiratory failure in cases of pulmonary embolism. Some of the newer pressor drugs, such as paredrine (p-hydroxy- $\alpha$ -methylphenylethylamine hydrobromide) or paredrinol (p-hydroxyphenylisopropylmethylamine sulfate), may prove even more suitable.

#### CONCLUSIONS

Dogs subjected to pulmonary embolism showed transient bronchoconstriction.

<sup>14</sup> Starr, I, Gamble, C J, Margolies, A, Donal, J S, Jr, Joseph, N, and Eagle, E. Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size, on Respiration, on Metabolic Rate and on the Electrocardiogram, *J Clin Investigation* **16** 799, 1937.

The available evidence indicates that bronchoconstriction is a reflex mediated over the vagus nerves and that the afferent impulses are dependent on a rise in pressure in the right chambers of the heart.

Drug therapy may have certain applications, although the clinical importance of the bronchospasm is still open to question. Atropine apparently prevents bronchospasm, while papaverine produces transitory constriction. Both drugs have been found useful in the treatment of pulmonary embolism and should be used. Digitalis in the form and dosage used has no appreciable effect on the bronchi. It can, and should, be used when there is auricular fibrillation or congestive heart failure without fear of possible harmful effects on the bronchi. Epinephrine should not be used as a bronchial antispasmodic because of the ready production of pulmonary edema following its administration.

The death of our experimental animals was usually due to respiratory failure. Failure of the respiratory center is complex and inextricably bound up with failure of the circulation. Therapeutic agents most likely to support both the circulation and the respiratory center appear to be (1) oxygen, (2) papaverine and (3) drugs capable of raising the systemic blood pressure without producing undesirable side effects. Ephedrine fulfils the last requirements reasonably well.

This work was done with the technical assistance of Miss Alice M. Lennon.

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# URINARY EXCRETION OF NICOTINIC ACID AND ITS DERIVATIVES

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Numerous studies have been made of the excretion of nicotinic acid and its derivatives in the urine, but as yet no satisfactory test has been devised for evaluation of the nutritional status of a person with regard to nicotinic acid. Deficiency is diagnosed on the basis of clinical findings. In view of the importance of nicotinamide in intermediary metabolism, a procedure is needed which will detect mild states of deficiency and indicate the degree of depletion in the tissues. Valuable contributions toward this end have been made by many investigators, including Melnick, Field and their collaborators<sup>1</sup> and Perlzweig and his co-workers<sup>2</sup>. Recently, Perlzweig, Sarett and Margolis<sup>3</sup> suggested that the urinary excretion following the administration of 500 mg of nicotinamide may serve as a test of nutritional condition in relation to nicotinic acid.

The object of this investigation was to study further the urinary excretion of nicotinic acid and its derivatives and, if possible, to devise a test which would assist in estimating the adequacy or deficiency of the supply of this vitamin in the human subject. Some of the findings were reported in a preliminary note<sup>4</sup>. Observations were made for 13 normal persons, 24 hospitalized

patients with various acute and chronic diseases and 26 patients with clinical evidence of deficiency of one or more members of the B group of vitamins. Thirteen of the patients in this last group had typical pellagra, 10 had symptoms of nicotinic acid deficiency without dermatitis, 2 had ariboflavinosis and 1 had polyneuritis due to lack of thiamine. The hospitalized patients without clinical evidence of deficiency disease were all members of the lower income group of the population, and their dietary histories often indicated an inadequate supply of the vitamin B complex. The diseases for which these persons entered the hospital were such that in many instances there may have been poor absorption or increased need of vitamins. The amount of nicotinic acid and its derivatives excreted was determined for each subject in one or more of the following circumstances: (1) in twenty-four hours with no administration of nicotinic acid or its derivatives, (2) in twenty-four hours after oral or parenteral administration of 100 mg of nicotinic acid, sodium nicotinate or nicotinamide, (3) in twenty-four hours after oral administration of 300 mg of nicotinamide, and (4) in six hours after oral administration of 300 mg of nicotinamide. Prior to each of these examinations, the patient was given a diet from which foods with high content of trigonelline (coffee, nuts and leguminous vegetables) were omitted. Such a diet is essential to the test, since nicotinic acid is excreted in the urine largely as trigonelline.

## METHOD

The method used for the determination of nicotinic acid and its derivatives was that of Perlzweig, Levy and Sarett<sup>2a</sup> with minor modifications, including several suggested by Dann and Handler<sup>5</sup>. Five to 20 cc. of urine, the amount depending on the probable concentration of nicotinic acid, was concentrated, hydrolyzed, adjusted to  $pH$  0.5 to 1, adsorbed on and eluted from Lloyd's reagent and treated with lead nitrate, as outlined by Perlzweig. The lead was removed by adding normal potassium phosphate ( $K_2PO_4$ ) until a permanent faint pink color was obtained with phenolphthalein as an indicator. After centrifugation, the supernatant fluid was poured off and the acidity adjusted to  $pH$  4.5, alkaline-acid test paper being used as an indicator.

Technical assistance was rendered by Herschel Welch, M S, Lillian Kyame, B S, and Shirley Cordill, B A.

From the Department of Medicine, School of Medicine, Tulane University and Charity Hospital of Louisiana.

Aided in part by a grant from the Eli Lilly Company to the Department of Tropical Medicine, Tulane University School of Medicine.

1 (a) Field, H, Jr, Melnick, D, Robinson, W D, and Wilkinson, C F, Jr. Studies on the Chemical Diagnosis of Pellagra (Nicotinic Acid Deficiency), *J Clin Investigation* **20** 379, 1941. (b) Melnick, D, and Field, H, Jr. Determinations of Nicotinic Acid by Means of Photoelectric Colorimetry, *J Biol Chem* **134** 1, 1940.

2 (a) Perlzweig, W A, Levy, E D, and Sarett, H P. Nicotinic Acid Derivatives in Human Urine and Their Determination, *J Biol Chem* **136** 729, 1940. (b) Sarett, H P, Huff, J W, and Perlzweig, W A. Studies in Nicotinic Acid Metabolism. I The Fate of Nicotinic Acid in Man, *J Nutrition* **23** 23, 1942.

3 Perlzweig, W A, Sarett, H P, and Margolis, L H. Studies in Nicotinic Acid Metabolism. V A Test for Nicotinic Acid Deficiency in Man, *J A M A* **118** 28 (Jan 3) 1942.

4 Goldsmith, G A. Evaluation of Nicotinic Acid Nutrition by Studies of Urinary Excretion, *Proc Soc Exper Biol & Med* **51** 42, 1942.

5 Dann, W J, and Handler, P. The Quantitative Estimation of Nicotinic Acid in Animal Tissues, *J Biol Chem* **140** 201, 1941.

The development of color with cyanogen bromide and paramethylaminophenol sulfate was carried out as indicated by Perlzweig<sup>2a</sup> except that 1 cc of 10 per cent potassium biphosphate ( $\text{KH}_2\text{PO}_4$ ) was added to each of the tubes. After one hour during which the tubes were kept in the dark to permit the development of color, readings were made in a Klett-Summerson photoelectric colorimeter, using a no 511 Corning filter. In each experiment a standard solution of nicotinic acid (containing 10 or 20 micrograms) was subjected to development of color. A reagent blank was prepared, as was a blank for the correction for residual color in the test solution obtained from urine.

In the determination of trigonelline the method of Perlzweig was followed, except that double the quantity of urea and alkali was used in most of the experiments. Larger amounts of trigonelline were recovered with this procedure, although the recoveries fell considerably short of those reported by Perlzweig.

The method for the determination of acid-hydrolyzable derivatives of nicotinic acid<sup>6</sup> was highly satisfactory. The average recovery of nicotinic acid added to urine in a series of 38 tests was  $98.03 \pm 1.98$  per cent. Nicotinamide was recovered equally well. The method for the determination of trigonelline, however, permitted recovery of only 40 to 50 per cent of the amount added. Nevertheless, repeated analyses of the same urine on different days and with samples of various sizes gave consistent results in most instances. The figures for trigonelline throughout this paper are given as nicotinic acid and represent the amount actually determined by analysis.

Urine was preserved with toluene, and if not tested immediately after collection it was autoclaved at 15 pounds' (68 Kg.) pressure for fifteen minutes, after the reaction had been adjusted to  $p_H$  7. In 13 experiments there was no loss when tests were repeated after two to thirteen days. Neither toluene nor sulfuric acid was a satisfactory preservative when urine was stored longer than twenty-four hours.

#### OBSERVATIONS

*Excretion of Nicotinic Acid and its Derivatives in the Urine in Twenty-Four Hours*—Studies were made on 10 normal persons and 37 hospitalized patients, of whom 12 had clinical evidence of nicotinic acid deficiency and 2 of ariboflavinosis. The nicotinic acid deficiency was complicated by peripheral neuritis in 1 patient and by a lack of riboflavin in 4 others. The results are given in the table. There was no difference in the amount of nicotinic acid (acid-hydrolyzable<sup>6</sup> derivatives) excreted by normal persons and by patients with or without deficiency disease. The amount of trigonelline excreted, however, was lowest in patients with pellagra and ariboflavinosis, highest in normal persons and intermediate in the hospitalized patients without obvious vitamin deficiency. The level of excretion of the 2 patients with evidence of only ariboflavinosis was as low as that of patients with lesions of both nicotinic acid and riboflavin deficiency. Since there is considerable overlap-

6 In the remainder of this paper, acid-hydrolyzable derivatives of nicotinic acid will be referred to as nicotinic acid.

ping of the findings for the three groups, estimation of the excretion of either trigonelline or total derivatives of nicotinic acid in a twenty-four hour specimen of urine is an unsatisfactory test of the adequacy of nutrition in relation to nicotinic acid in a given patient.

The figures listed in the table are corroborative of those of several other investigators. Perlzweig and his co-workers<sup>2b</sup> reported an average excretion of 1.2 mg of nicotinic acid and 15.1 mg of trigonelline in twenty-four hour specimens of urine for 33 normal subjects. In 12 hour specimens<sup>3</sup> the average output of trigonelline was 10 mg for normal persons and 7.7 mg for hospitalized patients. Field,<sup>1a</sup> using a different chemical method, found an average daily excretion of 3.8 mg of nicotinic acid and 19.5 mg of trigonelline for 10 normal persons, while for 7 subjects with vitamin deficiency the excretion of nicotinic acid averaged 2.7 mg and that of trigonelline 3.1 mg.

*Excretion of Derivatives of Nicotinic Acid in the Urine in Twenty-Four Hours*

Subjects	Number of Subjects	Nicotinic Acid,* Mg			Trigonelline, Mg			Total, Mg		
		Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
Normal	10	0.9	1.6	1.2	8.5	21.1	14.4	9.5	22.1	15.6
Hospitalized †	23	0.5	3.0	1.4	2.5	25.2	9.6	3.5	26.6	11.0
Vitamin deficient	14	0.1	1.6	1.0	1.1	21.4	8.4	1.2	22.8	9.4

\* Acid hydrolyzable derivatives of nicotinic acid.

† Hospitalized patients with no clinical evidence of deficiency disease.

*Excretion of Nicotinic Acid and its Derivatives in the Urine in Twenty-Four Hours Following the Administration of 100 mg of Nicotinic Acid, Sodium Nicotinate or Nicotinamide*<sup>7</sup>—Nineteen persons for whom the urinary excretion of nicotinic acid in twenty-four hours had been measured were given test doses of 100 mg. of nicotinamide parenterally (10 persons), sodium nicotinate parenterally (6 persons) or nicotinic acid orally (3 persons). Chart 1 shows the total excretion of derivatives of nicotinic acid (both nicotinic acid and trigonelline) in twenty-four hours after the administration of the test dose and also indicates the amount of the 100 mg dose which was recovered in this period obtained by subtracting from the total amount excreted the quantity present in the control twenty-four hour specimen. Normal persons excreted larger amounts of nicotinic acid derivatives after the test dose than did either group of hospitalized patients. Greater differences are observed if

7 The nicotinic acid, sodium nicotinate and nicotinamide were supplied by Merck and Company.

the total amount excreted in twenty-four hours after the test dose is considered rather than the extra amounts excreted. That is, the test dose magnifies the differences previously noted in the control measurement of the twenty-four hour excretion. This test, however, will not completely differentiate normal from deficient

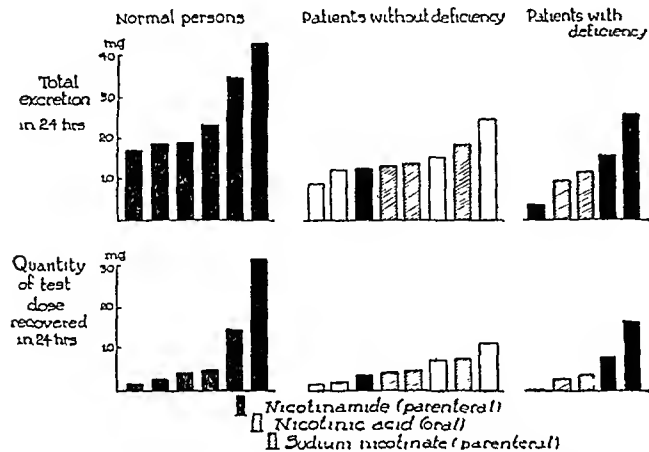


Chart 1—Urinary excretion of derivatives of nicotinic acid in twenty-four hours after a test dose of 100 mg of nicotinamide, sodium nicotinate or nicotinic acid

subjects. The output in 1 deficient patient (with ariboflavinosis) exceeded that of several normal persons. The 4 patients with pellagra excreted less than did the normal subjects, as did 6 of the 8 hospitalized patients without clinical signs of vitamin deficiency. The results were similar for each of the test substances administered, except that nicotinamide was excreted almost entirely as trigonelline, while sodium nicotinate and nicotinic acid increased the excretion of both trigonelline and acid-hydrolyzable derivatives of nicotinic acid.

**Excretion of Nicotinic Acid and its Derivatives in Twenty-Four Hours after the Oral Administration of 300 mg of Nicotinamide**—This test was performed on 31 persons, 10 normal subjects, 13 hospitalized patients without clinical evidence of deficiency disease and 8 patients with deficiency of the vitamin B complex (7 with nicotinic acid deficiency and 1 with ariboflavinosis). Chart 2 shows the total output of derivatives of nicotinic acid in twenty-four hours after 300 mg of nicotinamide was given orally. The quantity of the test dose which was recovered in this period is also indicated. The additional excretion was calculated by subtracting the amount excreted in the control period of twenty-four hours. Nine of the 10 normal persons excreted more than 40 mg of derivatives of nicotinic acid in the urine after the test dose. In only 1 patient with deficiency disease was the output above 40 mg. This subject had glossitis characteristic of an inadequate supply of nicotinic acid. About one half of the hospitalized patients without clinical evidence of

vitamin deficiency excreted more and the other half less than 40 mg. The figures which indicate the extra excretion, that is, the increment after the test dose, show a similar distribution. From normal persons, with 1 exception, 25 mg or more of the test dose was recovered, from deficient subjects, with the 1 exception already discussed less than 25 mg was recovered, while for hospital patients without vitamin deficiency the recovery in approximately half the instances was less and in half more than 25 mg. It appears to be unnecessary to measure the excretion in a control period. Measurement of the total excretion in twenty-four hours after the test dose gives information similar to that obtained from estimation of the quantity of test material recovered.

The findings reported here may be compared with those of Perlzweig, Sarett and Margolis,<sup>3</sup> who determined the extra excretion of total nicotinic acid in twelve hours after giving 500 mg of nicotinamide. They found that normal persons excreted a larger quantity of the test dose, than did undernourished subjects from a National Youth Administration camp, while a group of hospitalized patients excreted a still smaller amount. The studies of Perlzweig and his associates and those reported here suggest that the amount of the derivatives of nicotinic acid excreted after ingestion of a test dose of nicotinamide gives some indication of the state of nutrition in relation to nicotinic acid.

**Urinary Excretion of Nicotinic Acid and its Derivatives in Six Hours after the Oral Administration of 300 mg of Nicotinamide**—In view of

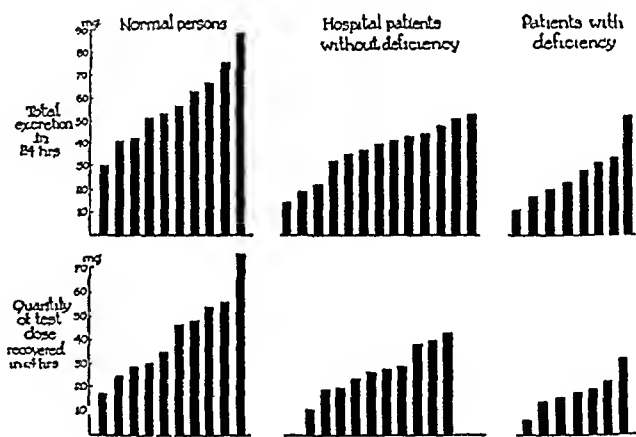


Chart 2—Urinary excretion of derivatives of nicotinic acid in twenty-four hours after the oral administration of 300 mg of nicotinamide

the difficulties involved in collecting twenty-four hour specimens of urine, the excretion in six hours was determined in 29 of the 31 subjects who received 300 mg of nicotinamide. It was found that the output of nicotinic acid and its derivatives in six hours measured approximately 50 per cent of the excretion in twenty-four hours.



(chart 3) The shorter test gives information comparable to that derived from the longer one

Accordingly, the quantity of derivatives of nicotinic acid excreted in the urine in six hours after the administration of 300 mg of nicotinamide was determined for 44 subjects, 13 normal persons, 13 hospitalized patients without vitamin

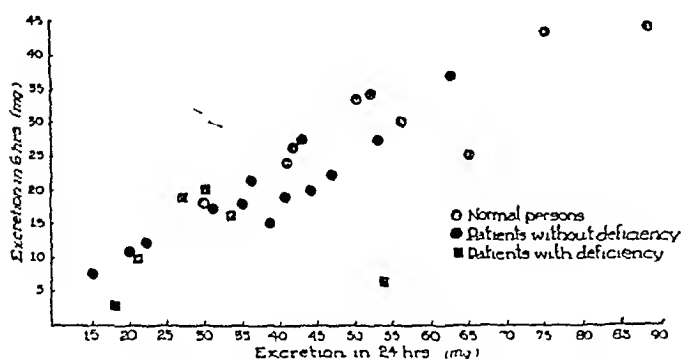


Chart 3—Comparison of urinary excretion of derivatives of nicotinic acid in six hours with that in twenty-four hours after the oral administration of 300 mg of nicotinamide

deficiencies and 18 patients with deficiency of the vitamin B complex. Eight of the deficient subjects had typical pellagra, 8 had nicotinic acid deficiency without dermatitis, 1 had thiamine deficiency and 1 had riboflavin deficiency. The nicotinic acid deficiency was complicated in 5 instances by ariboflavinosis and in 2 by peripheral neuritis due to lack of thiamine hydrochloride.

In performing the six hour excretion test it is essential to administer enough fluid to obtain a volume of urine of at least 200 cc. There is no quantitative relationship between the total excretion of nicotinic acid and the volume of urine, but when the output of fluid is extremely small the subject's maximum excretion of nicotinic acid may not be obtained. The results for the 44 persons who were given the six hour test are presented in chart 4. The minimum excretion for normal subjects after an oral test dose of 300 mg appears to be between 20 and 25 mg in six hours. Of 13 normal persons, only 2 excreted less than 23 mg. Repetition of the test on several occasions for 3 of the subjects gave results which checked within a few milligrams. Five of the hospitalized patients without evidence of deficiency disease excreted 20 mg or more in six hours, 8 excreted less than this amount. Fifteen of the 18 patients with clinical signs of deficiency of nicotinic acid and/or the other B vitamins excreted 20 mg or less in the test period. The amount excreted did not vary directly with the severity of the pellagra. A number of the hospitalized patients with acute and chronic disease excreted as small a quantity of nicotinic acid and its derivatives as did some patients with pel-

lagra. In all likelihood these findings indicate a subclinical nicotinic acid deficiency. The previous diet of these patients had been poor, and the intake, absorption and utilization of nutrients were complicated by organic disease. In other deficiency states, such as those due to an inadequate supply of thiamine or of ascorbic acid, laboratory tests often show diminished excretion of the respective vitamin prior to the appearance of clinical signs of deficiency. Similar findings might be anticipated in nicotinic acid deficiency.

The 3 subjects with clinical evidence of vitamin deficiency who had levels of excretion in the range of the normal subjects (above 20 mg) warrant comment. One had acute hepatitis following arsenical therapy for syphilis, the second had cirrhosis of the liver and the third had chronic alcoholism and polyneuritis. The first 2 patients had both glossitis and cheilosis, indicative of riboflavin and nicotinic acid deficiency, and, in addition, definite signs of severe hepatic disease. The third patient had evidence only of thiamine deficiency, and the bodily stores of nicotinic acid may have been adequate. Impairment of hepatic function may have been present in this patient also, in view of the history of chronic alcoholism, but special tests were not performed. The findings suggest the possibility that when hepatic function is abnormal the body may be unable to retain and utilize nicotinamide. However, many factors doubtless influence the excretion of nicotinic acid, and nicotinic acid is probably excreted in forms other than those which were measured with the chemical methods used.<sup>8</sup>

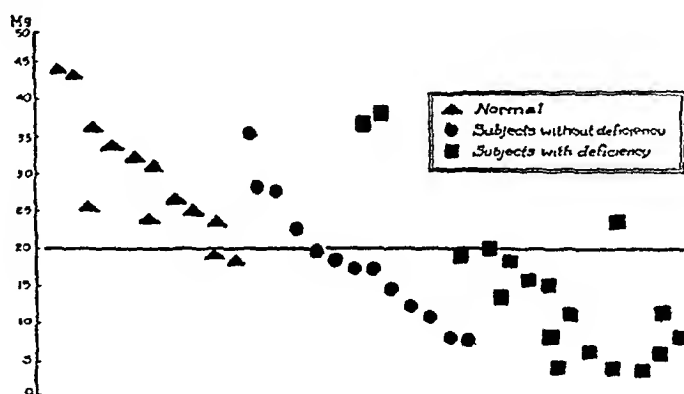


Chart 4—Urinary excretion of derivatives of nicotinic acid in six hours after the oral administration of 300 mg of nicotinamide

Two patients with pellagra<sup>9</sup> were given the six hour test of excretion of nicotinic acid at

8 Najjar, V. A., Stein, H. J., Holt, L. E., Jr., and Kobler, C. V. Excretion of Specific Fluorescent Substances in Urine in Experimental Nicotinic Acid Deficiency, *J. Clin. Investigation* 21:236, 1942.

9 The findings for these patients are not included in chart 4.

the time of entrance to the hospital and after a period of therapy, with nicotinic acid. One patient, a Negro woman aged 26, excreted 9.8 mg of derivatives of nicotinic acid when tested before any therapy was given. She received 300 mg of nicotinamide daily for four weeks. When retested at the end of this period, she excreted 16.3 mg. All evidence of pellagra had disappeared, except for pigmentation of the skin on the backs of the hands, and that was decreasing in intensity. The other patient, a white girl 10 years of age, excreted 8.8 mg of derivatives of nicotinic acid when the test dose was given shortly after admission to the hospital. She received 200 mg of nicotinic acid daily for three weeks, and repetition of the test showed an excretion of 11.9 mg. This patient was greatly improved at the time of the second test but still showed slight pigmentary changes. No nicotinic acid was given to either of these subjects for two days before the second test was performed. These data lend support to the validity of the six hour excretion test as a measure of the status of nutrition with regard to nicotinic acid.

## SUMMARY

The urinary excretion of nicotinic acid and its derivatives was studied for 63 persons under various experimental conditions. The total excretion of derivatives of nicotinic acid was greatest in normal persons, next highest in hospitalized patients without evidence of deficiency disease and lowest in patients with pellagra and vitamin B complex deficiency. This is true whether the output in twenty-four hours is measured or the output during various intervals after the administration of a test dose of nicotinic acid or nicotinamide. The difference in the total amount excreted by subjects in the three groups is due almost entirely to variations in the output of trigonelline. The administration of a large test dose of nicotinic acid, sodium nicotinate or nicotinamide magnifies this difference. Measurement of the quantity of derivatives of nicotinic acid excreted in six hours following the oral administration of 300 mg of nicotinamide is suggested as a useful procedure in evaluating the nutritional status of a person with regard to nicotinic acid.

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# SUBACUTE ENDOCARDITIS ASSOCIATED WITH INFECTION WITH A SPIRILLUM

REPORT OF A CASE, WITH REPEATED ISOLATION OF THE  
ORGANISM FROM THE BLOOD

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Clinical syndromes following rat bite have been ascribed to two micro-organisms, *Streptobacillus moniliformis* (*Streptothrix*, as originally described by Schottmuller) and *Spirillum minus*. The latter organism is of special interest in connection with the case about to be reported.

The present concept that rat bite fever is due to infection with a spirillum dates back to 1916, when Futaki, Takaki, Taniguchi and Osumi<sup>1</sup> described an unnamed spirochetal micro-organism as "the cause of rat-bite fever". One year later Futaki and his associates<sup>2</sup> termed this organism *Spirochaeta morsus muris*. On the basis of morphologic characteristics, especially the rigid body and the terminal flagellums, Robertson<sup>3</sup> preferred to classify the causal agent of rat bite fever (sodoku) as a spirillum. In view of the resemblance of the terminal flagellums to the minus sign, he proposed to adopt the name *Spirillum minus*, originally given by Carter,<sup>4</sup> for an organism isolated from a rodent.

The etiologic relation of *S. minus* to rat bite fever has been established beyond doubt, although the literature reveals that, at least in the United States, a disease with a clinical picture indistinguishable from that of rat bite fever is caused more frequently by *Str. moniliformis* than by the spirillum. Brown and Nunemaker<sup>5</sup> implied that some patients with rat bite fever may have been infected with both organisms.

From the Laboratories and the Second Medical Service of Dr. Eli Moschowitz, the Mount Sinai Hospital.

1 Futaki, K., Takaki, I., Taniguchi, T., and Osumi, S. The Cause of Rat-Bite Fever, *J. Exper. Med.* **23**:249-250, 1916.

2 Futaki, K., Takaki, I., Taniguchi, T., and Osumi, S. *Spirochaeta Morsus Muris*, N. Sp., the Cause of Rat-Bite Fever, *J. Exper. Med.* **25**:33-44, 1917.

3 Robertson, A. Observation on the Causal Organism of Rat-Bite Fever in Man, *Ann. Trop. Med.* **18**:157-175, 1924.

4 Carter, H. V. Note on the Occurrence of a Minute Blood Spirillum in an Indian Rat, *Scient. Mem. Med. Off. India*, 1887, pt. 3, p. 45.

5 Brown, T., and Nunemaker, J. C. Rat-Bite Fever. A Review of the American Cases with Re-evaluation of Etiology, Report of Cases, *Bull. Johns Hopkins Hosp.* **70**:202-327, 1942.

Cases of rat bite fever due to *S. minus* have occurred only endemically in the United States. One set of studies has been concerned with cases in which the diagnosis was made on the basis of a typical clinical picture and a definite history of rat bite. Among these cases were many in which the diagnosis was made by inoculation of laboratory animals (mice, rats and guinea pigs) with material from the lymph nodes<sup>6</sup> or the patient's blood<sup>7</sup> and subsequent dark field observation of the micro-organism in the blood of the inoculated animals. In several of these cases *S. minus* was observed on direct dark field examination of the patient's blood<sup>8</sup> and of material from the wound,<sup>9b</sup> and in some cases bacteriologic confirmation was not obtained.<sup>9</sup>

To another group of cases belong those in which the occurrence of an animal bite was either denied or not recognized.<sup>10</sup> Animal inoculations, however, proved that *S. minus* was the causative organism.

A review of the subject of rat bite fever leaves one with the impression that, despite positive reports, the isolation of *S. minus* from the patient's blood has thus far not been clearly successful. Bayne-Jones,<sup>11</sup> in 1931, quoted a personal communication from the Japanese investigators Futaki, Takaki, Taniguchi and Osumi.<sup>1</sup>

6 Gilkey, H. M., and Dennie, C. C. Rat-Bite Fever in Children, *South M. J.* **32**:1109-1111, 1939.  
Woolley, P. V., Jr. Rat-Bite Fever. Report of a Case with Serologic Observations, *J. Pediat.* **2**:693-696, 1936.

7 Lamb, A. R., and Paton, F. W. A Case of Vegetative Endocarditis Caused by Hitherto Undescribed Spirillum (*Spirillum Surati*, N. S.), *Arch. Int. Med.* **12**:259-272 (Sept.) 1913.

8 Low, C. G. A Case of Rat-Bite Fever in England, *Brit. M. J.* **1**:236, 1924. Lamb and Paton.<sup>7</sup>  
Rogliano, A. G. Two Cases of Rat-Bite Fever, *Surgery* **11**:632-635, 1942.

9 Arkin, A. Rat-Bite Fever. A Case Report, *West Virginia M. J.* **15**:281-284, 1920-1921. Gilkey and Dennie.<sup>6</sup>

10 Walker, H. Rat-Bite Fever. Report of Two Cases, *Virginia M. Monthly* **64**:272-275, 1937. Lamb and Paton.<sup>7</sup>

11 Bayne-Jones, S. Rat-Bite Fever in the United States, *Internat. Clin.* **3**:235-253, 1931.

in which they withdrew their previous claim of having been able to grow the spirillum on Shima-mine's medium. Attempts by Robertson,<sup>3</sup> Knowles and Das Gupta<sup>12</sup> and McDermott<sup>13</sup> to repeat Jodes's<sup>14</sup> cultivation of the micro-organism on a modified form of Vervoort's medium were never successful.

Foncannon<sup>15</sup> reported the cultivation of "*Spirochaeta morsus muris*" from the patient's blood in 1 case. He failed, however, to mention the method employed. In 1930 Douthwaite<sup>16</sup> reported that actively motile spirilla were observed from trypsinized bullock's heart inoculated with patient's blood. Mice were inoculated with the culture, and the micro-organism persisted in the peripheral circulation for a few days. In 1913 Lamb and Paton<sup>7</sup> isolated a spirillum from the blood of a patient with subacute endocarditis. They named the organism *Spirillum surati*, after the locality in India in which the disease was presumably contracted. It will be seen later that the ease with which the micro-organism grew after a short period of incubation makes its nature somewhat doubtful.

Recently, in Mount Sinai Hospital, we have had under study an unusual case of subacute endocarditis in which the causative micro-organism was *S. minus*. The causal relation of this organism to the endocarditis was suggested by clinical and serologic observations and was established bacteriologically. Pathologic and bacteriologic confirmation was obtained at autopsy. The relation of this micro-organism to the causative spirillum of rat bite fever was suggested by its morphologic characteristics, the serologic evidence and the behavior in mice.

#### REPORT OF CASE

A man aged 23 entered Mount Sinai Hospital (service of Dr. Eli Mosechowitz) on March 28, 1942.

**Past History**—The patient had worked on a tanker between Texas and New York and as a truck helper about freight yards. There was no history suggestive of syphilis, rheumatic fever or chorea. A Wassermann test of the blood made elsewhere was reported to give a negative reaction.

**Previous Illness**—About two months before his admission to the hospital the patient had fever, with a temperature of 105 F, and a pain in the right side of the chest. A physician made the diagnosis of pneu-

monia with pleurisy, and sulfonamide compounds were administered. The patient recovered.

Five weeks before admission to Mount Sinai Hospital he had a dizzy spell, followed by a chill, and his temperature rose to 103 F. He complained of headache, recurring spells of dizziness, stiffness of the neck and tenderness and pain in the left upper abdominal quadrant. These symptoms persisted for three days, and he was admitted to a hospital with the probable diagnosis of meningitis.

**Clinical Course** On admission (in February 1942) the temperature was 100.8 F and the pulse rate 95 a minute. The patient appeared acutely ill. The lungs were clear. The heart beat was regular, there were a loud, blowing systolic murmur at the apex, and a high-pitched diastolic murmur to the left of the sternum in the third intercostal space. The abdomen was moderately tender, with "splinting" in the left upper quadrant. The spleen was felt 1 fingerbreadth below the costal margin. The liver was palpable. Neurologic examination revealed no abnormality except for stiffness of the neck.

**Laboratory Data** The red blood corpuscles numbered 4,000,000, the hemoglobin measured 10.5 Gm per hundred cubic centimeters, and the white cell count was 8,000, with 55 per cent polymorphonuclear leukocytes and 34 per cent lymphocytes. The urine contained no protein or dextrose, agglutination tests of the blood serum gave negative reactions for typhoid and brucellosis, the test for heterophil antibodies gave a negative reaction. The Wassermann reaction of the blood was 4 plus, the Hinton reaction was positive, and the Kline reaction was 2 plus. Two spinal punctures were made. The first spinal tap induced trauma, the pressure was 160 mm of water, the reaction for globulin was 3 plus, the Wassermann reaction was 4 plus, and culture of the fluid yielded no growth. The second spinal tap yielded clear fluid, the pressure was not increased, the reaction for globulin was negative, the Wassermann reaction was 3 plus, and the colloidal gold curve was characteristic of dementia paralytica. There were no cells.

The patient's temperature dropped, and the headache and stiffness of the neck disappeared within three or four days after his admission. He was discharged on March 6 to the antisyphilitic clinic for treatment. It may be added that the serologic reactions of both parents were negative.

**Physical Status Prior to Admission to Mount Sinai Hospital**—The patient had already received several injections of a bismuth preparation before he consulted one of us (W. M. H.), on March 24. He complained of remittent malaise, chilliness and excessive perspiration. There was severe pain in the left thumb, and a small, nontender ecchymotic area was present over each ankle. An aortic diastolic murmur and an apical systolic murmur, radiating to the left axilla, were audible. Sediment from a centrifuged specimen of the urine contained a few red blood cells per high power field.

In view of the unusual prodromal course, the absence of a positive history of syphilis, the presence of the audible murmurs of aortic and mitral insufficiency, the firm spleen, which was palpable 2 fingerbreadths below the costal margin, the embolic lesions, the presence of occasional red blood cells in the urine and the relative well-being of the patient, the diagnosis of subacute bacterial endocarditis superimposed on rheumatic heart disease was made.

The positive Wassermann reaction was thought to be a pseudoreaction to the existing infection. With this

12 Knowles, R, and Das Gupta, B. M. Rat-Bite Fever as an Indian Disease, *Indian M. Gaz.* **63**: 493-512, 1928.

13 McDermott, E. N. Rat-Bite Fever. A Study of the Experimental Disease, with a Critical Review of the Literature, *Quart. J. Med.* **21**: 433-458, 1928.

14 Jodes, T. Cultivation of the Spirillum of Rat-Bite Fever, *Lancet* **2**: 1225-1226, 1925.

15 Foncannon, F. Rat-Bite Fever, *J. Kansas M. Soc.* **31**: 331-333, 1930.

16 Douthwaite, A. H. Rat-Bite Fever, *Guy's Hosp. Gaz.* **44**: 438-441, 1930.

diagnosis he was referred to the Mount Sinai Hospital for further study

*Clinical Course at Mount Sinai Hospital*—On the patient's admission to the hospital, the physical findings of the referring physician, described previously, were confirmed. The lesions of the ankle and thumb were no longer visible or palpable, and no other embolic lesions were present.

The provisional diagnoses were subacute bacterial endocarditis, possibly superimposed on rheumatic cardiovascular disease, and syphilitic aortitis, with aortic insufficiency to be ruled out.

The following clinical notes were taken during the patient's stay in the hospital.

March 30 The hemoglobin concentration was 87 per cent, the white blood cell count was 7,750, with 46 per cent segmented and 10 per cent nonsegmented polymorphonuclear leukocytes, 34 per cent lymphocytes, 7 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The Wassermann reaction of the blood was 4 plus and the Kahn reaction 3 plus. The specific gravity of the urine was 1.030, the urine contained no protein or sugar and only an occasional red blood cell. Culture of a specimen of blood taken at this time was reported to yield no growth four days later.

April 1 The sedimentation rate of erythrocytes by the Cutler tube method was 18 mm in one hour and six minutes, a normal value.

April 3 A roentgenogram of the chest revealed no abnormality of the heart or lungs. A specimen of the blood taken at this time and cultured in an atmosphere of 35 per cent carbon dioxide was reported six days later to be positive for a micro-organism resembling *S. minus*, the causative organism of rat bite fever.

April 7 The cerebrospinal fluid was clear and the pressure normal. The Pandy reaction was 4 plus, the reaction for globulin was plus-minus, the sugar content was 55 mg per hundred cubic centimeters, Wassermann reaction was negative, and the colloidal gold curve was 1111100000.

April 9 The Wassermann reaction of the blood was 4 plus, and the Kahn reaction, 3 plus. The tuberculin patch test gave a negative reaction. The Frei test was negative for lymphogranuloma venereum. A blood culture was reported positive six days later for a micro-organism resembling *S. minus*.

April 15 The diagnosis of subacute endocarditis due to infection with a spirillum was now suggested as an explanation for both the clinical course and the serologic reactions.

April 20 The patient complained of pain in the tip of the fourth finger of the left hand. The area was tender to pressure, but there were no external manifestations of embolism.

April 21 The optic disks were normal. An intravenous injection of 0.5 Gm of tryparsamide was given. A fourth blood culture was reported positive for *S. minus* six days later.

April 27 Prior to this date the patient displayed almost normal strength and was apparently free from symptoms, he often asked to be discharged. A painful area suddenly developed on the anterolateral aspect of the left ankle. There was no redness or edema at the site of maximum tenderness. A diagnosis of tenosynovitis of the tendons of the extensor muscles was made.

April 28 Neoarsphenamine, 0.1 Gm, was injected intravenously.

April 30 Neoarsphenamine, 0.2 Gm, was given intravenously.

May 2 Neoarsphenamine, 0.13 Gm, was given intravenously. The blood culture was reported negative for the spirillum twelve days later.

May 4 The hemoglobin was 82 per cent, and the white blood cell count, 6,300, with 45 per cent segmented and 14 per cent nonsegmented polymorphonuclear leukocytes, 34 per cent lymphocytes, 6 per cent monocytes and 1 per cent plasma cells.

May 5 Except for unusual axis deviation, the electrocardiogram was normal.

May 8 Neoarsphenamine, 0.4 Gm, was given intravenously.

May 9 The sixth blood culture was reported positive for *S. minus* five days later.

May 13 The Wassermann reaction of the blood was 4 plus, and the Kahn reaction 3 plus. Neoarsphenamine, 0.5 Gm, was given intravenously. The temperature rose to 102 F. It was observed that similar elevations, to between 101 and 102.8 F, had occurred previously at approximately thirteen to seventeen day intervals.

May 20 In view of the apparent ineffectiveness of neoarsphenamine, the five day continuous drip method of arsenical medication was begun, under the direction of Dr. L. Chargin. Half the therapeutic dose usually given to syphilitic patients, i. e., 0.12 Gm of mapharsen in 500 cc of 5 per cent dextrose, was administered, without febrile or other untoward reactions.

May 21 Mapharsen, 0.12 Gm in 500 cc of 5 per cent dextrose, was given intravenously. The hemoglobin concentration was 85 per cent, the white blood cells numbered 7,500, with 33 per cent segmented and 8 per cent nonsegmented polymorphonuclear leukocytes, 46 per cent lymphocytes, 10 per cent monocytes, 1 per cent eosinophils and 2 per cent basophils. The spleen was not tender and was enlarged to 2 or 3 fingerbreadths below the costal margin.

May 22 Mapharsen, 0.12 Gm in 500 cc of 5 per cent dextrose, was given intravenously. The hemoglobin concentration was 80 per cent, and the white blood cells numbered 4,500, with a differential count similar to that on the preceding day.

May 23 Mapharsen, 0.12 Gm in 500 cc of dextrose, was given intravenously. The hemoglobin concentration was 79 per cent, and the white blood cells numbered 6,200.

May 24 Mapharsen, 0.12 Gm, in 500 cc of dextrose, was given intravenously.

May 25 A blood culture was reported to be negative for the spirillum ten days later.

May 26 Despite the administration of 0.6 Gm of mapharsen within five days, the serologic reactions remained unchanged.

May 28-30 In the midst of the patient's apparent "good health," pain suddenly developed in the left upper abdominal quadrant and the left shoulder. This was attributed to a splenic infarct, probably at the upper pole. It served to indicate that an active valvular process was still smoldering, despite the negative report on the last blood culture. The spleen was not tender, nor had it increased significantly in size. Although the urine had almost continuously shown varying traces of protein and microscopic evidence of blood, the incident of pain was the first clearcut evidence of visceral embolization observed in the hospital.

June 2 The blood culture was reported positive for *S. minus* six days later.

June 9 The blood culture was reported positive for *S. minus* six days later.

June 12 Two small circular erythematous macules, about 5 mm in diameter, were noted on the outer aspect of the sole of the left foot

June 13 Because the usual antisyphilitic arsenicals were ineffective in altering the clinical course and the positive blood culture, 1 Gm of tryparsamide was administered intravenously, at the suggestion of Dr Chargin

June 15 Three small round, tender macules appeared on the sole of the left foot Again, severe pain in the left upper abdominal quadrant radiated to the left shoulder and was intensified by deep breathing The spleen was now tender

June 16 A tender, erythematous lesion appeared under the nail of the third right finger The highest

June 22 Pulmonary edema developed, and the patient died

**Bacteriologic Data**—Cultivation of *S minus* from the Blood Ten specimens of blood were taken for culture They were obtained at the bedside in the following routine manner <sup>17</sup> Twenty-three cubic centimeters of the patient's blood was drawn from an anterior cubital vein Fifteen cubic centimeters was divided equally among three 100 cc Erlenmeyer flasks, the first containing veal infusion broth,  $p_H$  7.4, the second, 2 per cent dextrose-veal infusion broth,  $p_H$  7.4, and the third, 10 per cent tomato extract-veal infusion broth,  $p_H$  7.6<sup>18</sup> The remaining 8 cc of blood was equally divided to form three pour plates Two cubic centimeters was mixed with each of two tubes con-

TABLE 1—*Bacteriologic Data on Blood Cultures in a Case of Rat Bite Fever*

Blood Culture		Mediums Used *	Mediums in Which Micro Organism Grew *	Length of Incubation, Days	Specimen Taken, Day After Treatment	Treatment Employed
Date	No					
3/30	1	Routine	No growth	4, under aerobic and anaerobic conditions		None
4/ 3	2	Routine	1 2% dextrose flask, 1 tomato flask	6, in approximately 3 5% carbon dioxide and under anaerobic conditions		None
4/ 9	3	Routine	1 2% dextrose flask, 1 tomato flask	6, in approximately 3 5% carbon dioxide and under anaerobic conditions		None
4/21	4	Routine	1 2% dextrose flask, 1 tomato flask	6, in approximately 3 5% carbon dioxide and under anaerobic conditions		None
5/ 2	5	1 plain flask, 2 2% dextrose flasks, 2 tomato flasks	No growth	12 in approximately 3 5% carbon dioxide	Third	4/21 Tryparsamide, 0.5 Gm intravenously 4/28 Neoarsphenamine, 0.1 Gm, intravenously 4/30 Neoarsphenamine, 0.2 Gm, intravenously
5/ 9	6	3 2% dextrose flasks, 2 tomato flasks	1 2% dextrose flask, 1 tomato flask	5, in approximately 3 5% carbon dioxide	First	5/2 Neoarsphenamine, 0.3 Gm, intravenously 5/8 Neoarsphenamine, 0.4 Gm, intravenously
5/25	7	2 2% dextrose flasks, 3 tomato flasks	No growth	11, in approximately 3 5% carbon dioxide	First	5/13 Neoarsphenamine, 0.5 Gm, intravenously 5/20 Mapharsen, 0.12 Gm in 500 cc of 5% dextrose 5/21, 5/22, 5/23 and 5/24 Mapharsen, 0.12 Gm in 500 cc of 5% dextrose
6/ 2	8	2 2% dextrose flasks, 3 tomato flasks	1 tomato flask	9, in approximately 3 5% carbon dioxide		None
6/ 9	9	2 2% dextrose flasks, 3 tomato flasks	3 tomato flasks	6, in approximately 3 5% carbon dioxide		6/13 Tryparsamide, 1.0 Gm, intravenously
6/18	10	2 2% dextrose flasks, 3 tomato flasks	No growth	18 in approximately 3 5% carbon dioxide	Fifth	6/20 Tryparsamide, 2 Gm, intravenously

\* The mediums containing 2 per cent dextrose and 10 per cent tomato extract were made up with veal infusion broth

temperature for the past seventeen days was 100.6 F. An abnormal sedimentation rate of twenty minutes was reported. The Wassermann reaction of the blood was 4 plus, and the Kahn reaction was 1 plus.

June 18 The temperature rose to 103.8 F. Two tender, violaceous, slightly raised lesions, of 0.5 inch (1.27 cm) diameter, appeared on the hypothenar eminence of each hand. The tenth blood culture was reported negative for *S minus* eighteen days later.

June 19 The white blood cell count was 7,250.

June 20 Tryparsamide, 2 Gm, was given intravenously.

June 21 A fresh petechia was noted over the right external malleolus. There suddenly developed pain in the occiput, nausea, projectile vomiting, painful flexion of the neck and a rise in blood pressure to 220 systolic and 70 diastolic. It was the clinical impression that the patient had sustained a subarachnoid hemorrhage

taining 12 cc of 2 per cent dextrose-veal infusion agar,  $p_H$  7.4, 2 cc was mixed with a tube containing 12 cc of plain veal infusion agar,  $p_H$  7.4, and 2 cc was put into a tube containing 10 cc of cooked liver broth,  $p_H$  7.4, which was sealed with 2 cc of sterile petrolatum. Gram stains of samples from the flasks were made each day.

As is shown in table 1, the first specimen of blood, which was incubated under aerobic and anaerobic con-

17 Schwartzman, G, and Goldman, J. L. *Streptococcus Haemolyticus Bacteremia*, Arch Surg 34 82-98 (Jan) 1937.

18 Schwartzman, G. Food Accessory Substances in Bacterial Growth, Proc Soc Exper Biol & Med 22 7-9, 42-44 and 44-47, 1924. Thjotta, T, and Avery, O. T. Studies on Bacterial Nutrition, J Exper Med 34 97-114, 1921. Schwartzman and Goldman <sup>17</sup>



ditions, remained sterile during the four days of observation. The second, third and fourth samples of blood were cultured in the routine manner except that they were placed in an atmosphere of air containing approximately 35 per cent carbon dioxide<sup>19</sup>. This atmosphere was obtained by placing a lighted candle in a glass jar fitted with a petrolatum-sealed cover. On the sixth day of incubation gram-negative and gram-positive spiral micro-organisms were observed on stained spreads from the 2 per cent dextrose-veal infusion broth and the 10 per cent tomato extract-veal infusion broth.

Because it became apparent from a study of the initial blood cultures that the micro-organism grew only in liquid mediums, the fifth and the subsequent specimens



Fig 1—Photomicrograph of a spread of material taken from the 10 per cent tomato extract-veal infusion broth containing the ninth blood culture after eight days of incubation, showing blood cells and *S minus*, the organisms being of variable lengths.  $\times 1,200$ , Gram stain.

of blood taken for culture were placed only in 2 per cent dextrose-veal infusion broth and 10 per cent tomato extract-veal infusion broth and incubated in an atmosphere of 35 per cent carbon dioxide. The fifth specimen of blood, culture of which was sterile in all mediums, was taken after tryparsamide and neoarsphenamine had been administered over a period of eleven days. The arsenical therapy did not prove effective, however, for culture of the sixth specimen, taken twenty-four hours after an intravenous course of neoarsphenamine, yielded

19 Haynes, E. The Importance of Culturing Hemolytic Streptococci Under Increased Carbon Dioxide Tension, *Am J Clin Path, Tech Supp* 6 55-56, 1942.

growth after only five days of incubation. Although culture of the seventh sample of blood, which was taken after mapharsen therapy, did not reveal *S minus*, culture of subsequent samples yielded the organism. Culture of blood taken four days before death, however, gave negative results.

The micro-organism grew in the presence of carbon dioxide on the first transplant from the original blood culture flasks to a 2 per cent dextrose-veal infusion broth flask and a 10 per cent tomato extract-veal infusion broth flask. Three to 5 cc of citrated human or rabbit blood was added to each of the flasks used for the transplant. Without the addition of blood, a second serial transplant yielded growth in these fluid mediums. After a third passage the organism failed to grow. By addition of citrated human blood to the 2 per cent dextrose-veal infusion broth and the 10 per cent tomato extract-veal infusion broth, the micro-organism was successfully carried for eighty genera-



Fig 2—*Treponema recurrentis* in the blood in a case of relapsing fever in man.  $\times 1,400$ , Wright stain.

The morphologic features clearly differentiating this organism from *S minus* are the greater length and a number of regular primary waves of notably wider amplitude.

tions, over a period of eleven months, before it finally died. When first isolated, the spirillum grew only in an atmosphere of 35 per cent carbon dioxide. After five months of transplantation, the micro-organism grew aerobically.

All attempts to subculture the micro-organism on Nichols, Novy and MacNeal agar, semisolid mediums, gelatin mediums, chocolate blood agar plates, plain agar plates and blood agar plates proved futile. This result agrees with the work of McDermott,<sup>13</sup> Robertson<sup>3</sup> and Steiner.<sup>20</sup>

20 Steiner, W. R. A Case of Rat-Bite Fever, *Tr Am Clin & Climatol A* 46 1-5, 1930.

Each of 4 mice received an intraperitoneal injection of 1 cc of the second positive blood culture in the 10 per cent tomato extract-veal infusion broth. The animals remained in good condition for ten days. Peritoneal washings obtained by a capillary tube were examined by means of Gram-stained spreads. The spirillum was seen in the peritoneum on the fifth and seventh days after inoculation and disappeared from the peritoneum on the ninth day. On the fifth day 1 mouse was killed, and the spirillum was demonstrated on a spread of the heart's blood stained by the Gram method.

**Morphologic Characteristics of *S. minus*** Dark field illumination of washings of the mouse peritoneum and of the blood culture suspension yielded identical pictures. Actively motile spirilla were seen moving rapidly across the field. The micro-organisms seemed rigid throughout their length, they moved forward in spiral fashion, while turning about on their longitudinal axis without bending.

taken by Dr Gregory Schwartzman, illustrate the spirillum described.

**Examination of Specimens from the Patient Other than the Blood** Cultures taken of material from the bases of the teeth and of the urine and the cerebrospinal fluid failed to reveal the presence of spirilla. The sediments of two specimens of cerebrospinal fluid, which had been centrifuged for ten minutes, were negative for spirilla on dark field examination and in spreads stained by the Gram method. A specimen of urine obtained when the patient's temperature was 102 F and centrifuged ten minutes was also negative for the spirillum on dark field examination and in spreads stained by the Gram method.

**Postmortem Observations** A spread of the blood taken from the heart at autopsy and stained by the Gram method revealed the spirilla. Crushings of the vegetations stained by the Gram method showed the spirilla clumped together in large masses.

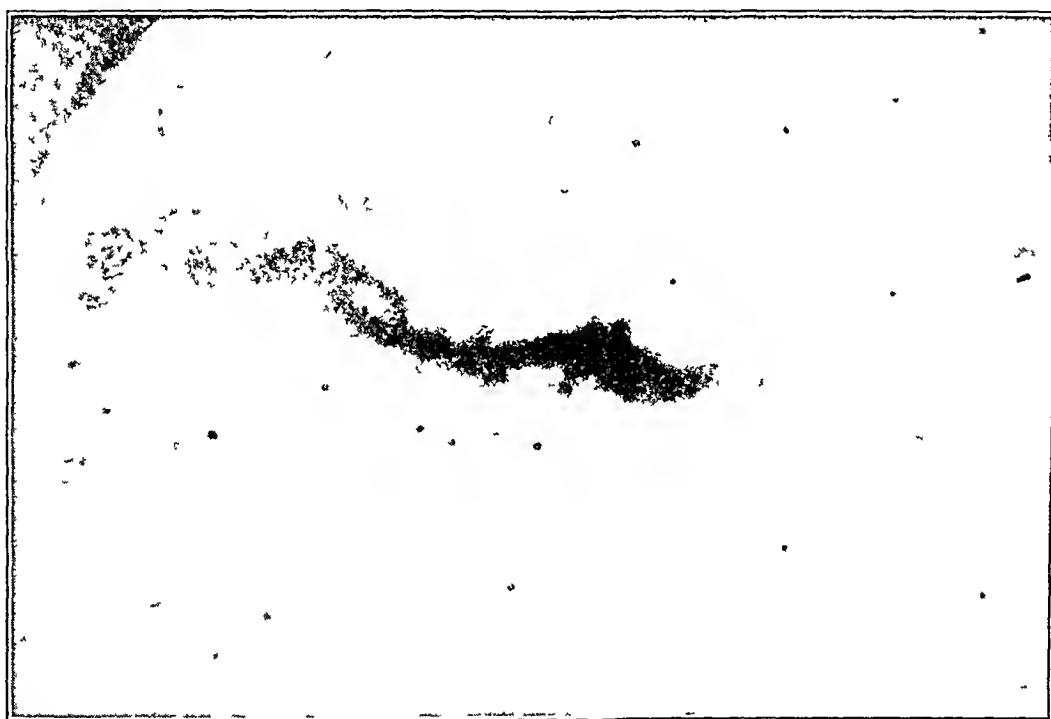


Fig 3—Electron micrograph (Dr Gregory Schwartzman) Magnification with the electron microscope, 8,000, photographic magnification, 375, total magnification, 30,000

A centrifuged specimen of growth from a blood culture was washed in Locke-Ringer solution. A drop of a light suspension was dried on the surface of a collodion film. The dried film was quickly washed by the method of Anderson and Mudd and dried in the air before it was mounted on the target.

The complex structure of an undulate body is suggested by the photograph. In particular, the processes on the side and at the end of the main body are to be noted. The end process possibly is responsible for the appearance of the minus sign described by previous authors.

A Gram stain of the blood culture suspension and the peritoneal washings revealed gram-positive and gram-negative micro-organisms, of varying sizes and shapes. Generally, the length of the spirillum ranged from one-half to twice the diameter of an erythrocyte. The undulations were shallow and few, which imparted a slender, short appearance to the micro-organism. The ends of the spirilla were distinct. They were either straight or tapered, one end being longer than the other. The Giemsa stain revealed no new morphologic structures, the organism exhibiting a slender, beaded appearance with shallow undulations.

A photomicrograph of the *S. minus* and, for comparison, one of the *Treponema recurrentis* from a recent case in man, as well as an electron micrograph,

**Serologic Studies—Agglutination Test of Patient's Serum** Agglutination tests for the enteric group of organisms, *Brucella abortus* and *Brucella melitensis*, gave negative reactions. The agglutination test for heterophil antibodies gave positive results in 1:16 and 1:32 dilutions.

**Serologic Reactions** In addition to the serologic tests performed at the Mount Sinai Hospital, similar tests were performed by another laboratory, by arrangement with Dr Chargin, during the patient's stay at the hospital.

The paradoxical behavior of the serologic tests, as seen in tables 2 and 3, and the presence of an aortic lesion seemed to favor the assumption of a syphilitic infection. There was, however, no history of a primary lesion or

of a secondary eruption, and at autopsy the pathologic observations were negative for syphilis

As seen in table 3, the positive reactions of the cerebrospinal fluid for syphilis reported from another hospital could not be confirmed at the Mount Sinai Hospital. This reaction must be regarded as a laboratory error or as a false positive reaction, which is known to occur with certain diseases (tumors and various forms of meningitis)

*Postmortem Examination*—The body was that of a well developed, well nourished, tall, muscular white man. Over each hypothernar eminence was a round hemorrhagic area, 3 mm in diameter.

*Thorax* Each pleural cavity contained about 50 cc of clear fluid.

*Heart* The pericardial sac contained no excess fluid. The heart was moderately enlarged and weighed 460 Gm. The tract of outflow of the right ventricle and the trabeculae carneae were slightly thickened. The left auricle was slightly thickened, its appendages contained no thrombi. The free edge and the line of closure of the mitral valve were distinctly thickened, and the thickened free edge overhung the chordae tendineae in

appearance of some of the verrucae on the posterior leaflet of the mitral valve. The wall of the left ventricle was hypertrophied, and the trabeculae carneae were massive. The cusps of the aortic valve were moderately thickened, and their free edges appeared rolled. This was particularly evident in the posterior cusp, where thickening of the free edge had produced shortening of the cusp. There was slight fusion at the commissures between the left and the right anterior cusp and between the posterior and the left anterior cusp. It cannot be said, however, that there existed a real anatomic insufficiency of the aortic valve. Over the nodule of Arantius of the right anterior cusp was a ragged, fleshy group of vegetations the size of a pinhead. The myocardium was pale red. The coronary arteries were widely patent and showed no sclerosis. The ostium of the right coronary artery was smaller than usual. There were two minute accessory coronary ostia. The aorta was smooth and elastic. There was significant atheromatous flecking of the coronary sinuses.

*Lungs* The lungs weighed 1,600 Gm and were large and heavy. The pleural surfaces were smooth and

TABLE 2—Serologic Data on the Blood

Examination	Wassermann Test	Hinton Test	Kahn Diagnostic Test	Kahn Verification Test	Kline Diagnostic Test	Kline Exclusion Test	Mazzini Test
Draft board	—						
Another hospital, 2/42	4+	+					
Mount Sinai Hospital, 3/30	4+		3+				
4/9	4+		3+				
5/13	4+		3+				
6/16	4+		1+				
Another laboratory, 5/2	Anticomplementary				3+	4+	2+
5/7	Anticomplementary		4+ 40 units	Syphilitic type of verification reaction	3+	4+	3+

shelflike fashion. The chordae tendineae at their insertion into the anterior and the posterior leaflets of the mitral valve were also thickened and fused. An irregular row of vegetations was present along the line of closure and along the free edge of both mitral valves. These vegetations were pink and fleshy, and their diameters varied from 1 mm to 0.5 cm. They extended downward onto the chordae tendineae. On the posterior

glistering. The trachea and bronchi oozed large quantities of sanguineous foam. The cut surfaces were moist and contained a good deal of blood. There were no areas of consolidation. The pulmonary vessels were normal.

*Liver* The liver was large and weighed 2,400 Gm. Its surface was smooth and glistening and showed brownish red to brown mottling. On section it had the appearance of chronic passive congestion, with irregular distribution of blood. The gallbladder, the bile ducts, the portal vein and the hepatic artery were normal.

*Pancreas* The pancreas was moderately firm. On section it appeared normal but was congested and tawny. The pancreatic ducts were not dilated.

*Spleen* The spleen was large, flabby and rather long. It weighed 700 Gm. The surface was smooth, glistening and gray, except for one large, slightly bulging area near the lower pole, which had a dark red and yellowish mottling. This area evidently represented a large infarct, which on section appeared wedge shaped, necrotic and yellowish. The spleen was extremely pulpy when sectioned elsewhere. The pulp was purplish and oozed from the cut surface. After the purplish, diffuent pulp was removed with a sponge, the spleen presented an unusual appearance. It was studded with innumerable whitish nodules, 2 to 3 mm in size, many of which appeared confluent. The nodules were much larger than the usual follicles, and on close examination it was suspected that the central portions of many

TABLE 3—Data on the Spinal Fluid in a Case of Rat Bite Fever

Examination	Wassermann Reaction	Colloidal Gold Curve	Reaction for Globulin
Another hospital			
First puncture	4+		3+
Second puncture	3+	Paritic	—
Mount Sinai Hospital, 1/7	—	—	±

leaflet, one vegetation presented a yellowish, cheesy, friable appearance. The aortic aspect of the anterior leaflet of the mitral valve presented near its center a large oval lesion, which measured 18 by 6 mm. A shallow ulceration occupied the center of the lesion, whereas the periphery was composed of a ring of verrucae surrounding the central ulceration, so that the whole lesion resembled an atoll. The peripheral verrucae were flat and fleshy, but at the lower edge they were larger and had the same yellowish, friable, cheesy

whitish nodules were somewhat grayish and more opaque, an appearance suggestive of the original follicles. In the area adjacent to the infarct the red pulp was much firmer and was deeply congested, and the true follicles were more evident. These follicles were smaller than the white nodules already described. The splenic artery and vein were normal.

**Gastrointestinal Tract** Except for congestion, the esophagus, stomach and intestinal tract presented nothing unusual. In the midportion of the mesentery of the small intestine, a large nodule, of hazelnut size, was observed along the course of one of the mesenteric arteries. Section of the nodule exposed a saccular aneurysm, with a thin wall on one side and a crescentic, lamellated wall on the opposite side. The involved vessel was easily probed, and no occlusion proximal or distal to the aneurysm could be demonstrated. The small intestine supplied by this altered mesenteric artery presented no gross abnormality.

**Genitourinary Tract** The kidneys were similar in size and appearance and together weighed 360 Gm. The capsules stripped with ease, with exposure of a smooth, reddish surface. No petechiae or hemorrhages were seen. A few scattered, small, flat, stellate dark depressions were noted in the cortex. Several small round, yellowish white areas, 2 to 3 mm in diameter, were discerned on the surface. These extended into the center for a distance of 2 to 3 mm. On section the architecture of the kidney was not unusual. The cortex was of normal width. The glomeruli were not clear. The medullary markings were normal. The renal pelvis and ureters were normal. The urinary bladder, prostate, seminal vesicles, testes and epididymides appeared grossly normal.

**Adrenal Glands** The adrenals were normal in size and shape. The yellowish cortex was congested.

**Bone** A lumbar vertebra showed a moist, red, finely spongy marrow.

**Microscopic Examination**—**Heart** A Gram stain of a section through a vegetation on the mitral valve showed granular, rod-shaped and comma-shaped coccoid bodies (the latter being considerably smaller than ordinary cocci). This granular material was gram-positive. The base of the vegetation showed organization, as seen in cases of subacute endocarditis due to *Streptococcus viridans*. Section of the myocardium of the left ventricle (hematoxylin-eosin stain) demonstrated numerous ill defined, fibrotic and hyalinized perivascular areas. A few scattered myocardial areas presented fully developed Aschoff bodies.

**Lungs** Edema and congestion were pronounced, occasional heart failure cells were present.

**Liver** Edema was marked. There were prominent Kupffer cells and slight lymphocytic infiltration in the periportal areas.

**Spleen** Examination revealed acute infectious splenitis, with multiple foci of small infarcts.

**Pancreas** Scattered foci of lymphocytic infiltration occurred within the acini, with atrophy of the acinar tissue.

**Adrenals** Severe congestion and an acute mycotic aneurysm of a small artery of the adrenal capsule were noted.

**Kidneys** Sporadic acute focal embolic glomerular lesions were present, some of which were fibrotic. Scattered glomeruli were completely fibrosed. These altered glomeruli were often surrounded by zones of lymphocytes. Small foci of abscess-like lesions were noted in the cortex.

**Mesenteric Artery** A mycotic aneurysm with organizing thrombus was noted.

**Summary of Anatomic Observations**—The anatomic changes were subacute bacterial endocarditis of the mitral and aortic valves, rheumatic heart disease, chronic interstitial valvulitis of the aortic and mitral valves, rheumatic myocarditis (Aschoff nodules), mycotic aneurysm of a branch of the superior mesenteric artery, hypertrophy of the right and left ventricles (moderate), infectious splenitis, splenomegaly and subacute splenic infarct, pulmonary congestion and edema, and chronic passive congestion of the liver.

#### COMMENT

The clinical course was similar to that usually encountered in cases of subacute bacterial endocarditis. The classic features of the latter condition observed in this case were low grade fever with occasional increases in temperature, endocardial murmurs, splenomegaly, multiple visceral and subcutaneous embolization, microscopic hematuria, petechiae, Osler and Janeway lesions and subarachnoid hemorrhage as a terminal event. That the endocarditis was subacute was clearly established by its long duration, i. e., an interval of nineteen weeks from the earliest febrile episode to the termination of the illness.

The isolation of *S. minus* from the blood culture led to considerable speculation as to the cause and pathogenesis of the endocarditis. At first, there was doubt as to the etiologic role of the micro-organism identified as *S. minus*, since there was no history of rat bite. On closer investigation it was found that the food ingested by the patient at the water front was exposed to rats and wild cats. The patient also had direct contact with alley cats, a fact which might be significant since a case of rat bite fever following a cat bite<sup>21</sup> has been reported.

It is of interest at this point to mention Mooser's<sup>22</sup> work, which revealed on anatomic grounds that the pathway of transmission is not necessarily through contact with the blood of the infected rat. According to this author, the invariable presence of keratitis in the afflicted animals may be responsible for the following method of spread of the disease.

The spiral micro-organism passes through the lacrimal channel into the nasal cavity and hence may enter the mouth, though its presence there is not absolutely necessary for transmission through bites. The upper lip of the rat is cleft and since the biting animal touches the bitten object with the nose, the organism may enter the wound from this point.

In our case it is assumed that the skin or the gastrointestinal tract was the possible portal of

21 Mock, H. E., and Morrow, A. R. Rat-Bite Fever Transmitted by Cat-Bite, Illinois M. J. **61** 67-70, 1932.

22 Mooser, H. Experimental Studies with a Spiral Organism Found in a Wild Rat, J. Exper. Med. **39** 589-602, 1924.

entry That the micro-organism isolated was identical with that of rat bite fever was confirmed by its morphologic structure, its cultural characteristics and its power to invade mice The etiologic significance was clearly established by six repeatedly positive blood cultures during a period of two months, the absence of any other organisms in the blood cultures and the demonstration of the organism in the crushings of the vegetations removed post mortem The positive serologic reactions provided additional indirect evidence that the micro-organism causing the endocarditis in this case was *S* minus<sup>5</sup>

It is doubtful whether this micro-organism bears any resemblance to the spirillum isolated from the blood in Lamb and Paton's<sup>7</sup> case of subacute endocarditis caused by a spirillum The striking biologic differences of the two spirilla are evident from the following summary

	Lamb and Paton's Case	Our Case
Blood culture	Organism grew aerobically, growth appeared in 5-6 days	Organism grew in 3.5% carbon dioxide, growth appeared in 5-9 days
Subcultures	Successive transplants grew in 24 hours	Successive transplants required human citrated blood and 3.5% carbon dioxide, growth appeared in 5-6 days
Serologic reactions	Wassermann reaction negative	Wassermann, Kahn and Kline reactions positive

The cultural dissimilarity of the micro-organisms, as well as the difference in their serologic reactions in man, offers supporting evidence that the two strains are quite different

The absence of a cutaneous rash does not mitigate against the assumption that rat bite fever, rather than the endocarditis, was the initial illness, the subacute endocarditis supervening at a later stage The early history was vague, and the type of rash invariably observed in the early exacerbations of rat bite fever could well have been mild enough to be overlooked Certainly even the periodicity of the fever suggests the trend toward "relapsing" elevations of temperature described in cases of rat bite fever

The presence of lesions in the heart gave support to the clinical impression that the patient was suffering from chronic rheumatic disease of the mitral and aortic valves, on which was superimposed subacute verrucous endocarditis due to infection with a spirillum The absence of clinical and roentgenographic evidence of significant cardiac enlargement, as well as the absence of evidence of a murmur of aortic insufficiency during examination by the draft board one year before, can be satisfactorily explained on the basis of the postmortem observations Careful examination of the aortic valves revealed fusion of the commissures of the cusps, but no significant aortic incompetence could be demonstrated anatomically The hemodynamic evidence of aortic

insufficiency probably appeared later, as a result of the vegetations on the aortic valves due to infection with the spirillum, which must eventually have interfered with the competent closure of the ostium of the valves during diastole The patient did not live long enough, however, to manifest the classic enlargement of the left ventricle associated with disease of the aortic valves

Mycotic aneurysms of the type observed in segments of the superior mesenteric and the adrial arteries are frequently encountered with bacterial endocarditis A similar lesion was undoubtedly present in a cerebral artery and led to the terminal subarachnoid hemorrhage

There was neither gross nor microscopic post-mortem evidence to substantiate a clinical or a serologic diagnosis of syphilis Although, from a theoretic standpoint, anatomic corroboration

is unnecessary for the diagnosis of syphilis in a patient of the age of this man, the negative evidence at autopsy and the fact that a high percentage of false positive serologic reactions have been reported in cases of infections with the spirillum<sup>6</sup> should serve as evidence sufficient to refute the diagnosis of a coexisting hidden syphilitic infection

Arsenicals were employed without success Despite their therapeutic efficiency in cases of rat bite fever, they exerted little, if any, effect on the growth and dissemination of the spirilla in this case of verrucous endocarditis The patient received a total of 1.5 Gm of neoarsphenamine A negative blood culture for the spirillum was obtained after completion of neoarsphenamine therapy and another after administration of mapharsen was finished A third negative culture was obtained four days before the patient's death, even though the crushings from the valves, obtained post mortem showed an abundance of the micro-organisms Negative blood cultures are frequently observed in cases of subacute bacterial endocarditis, and their occurrence in this case must also be regarded as accidental rather than as a temporary effect of the arsenicals employed

This case emphasizes the importance not only of cautious interpretation of serologic tests but of accurate anatomic localization of existing valvular murmurs It is true that syphilis may

occur at any age, but the diagnosis of acquired aortic insufficiency of syphilitic origin at the patient's age is open to question. It was the unfortunate combination of a false positive Wassermann reaction and an audible murmur of aortic insufficiency that led able clinicians to ignore a coexisting loud blowing apical systolic murmur of mitral insufficiency, which, if it had been evaluated properly, would have led to question of the validity of the diagnosis of syphilis. In this instance, the patient would have been spared much unhappiness and embarrassment if he had not erroneously been stigmatized as syphilitic.

#### SUMMARY

In a case of subacute endocarditis due to *S. minus*, the etiologic micro-organism of rat bite fever was isolated six times from the blood in

dextrose and tomato bouillon and grown in an atmosphere of 3.5 per cent carbon dioxide. Its relation to the causative organism of rat bite fever was established by its morphologic characteristics, its pathogenicity and serologic effects in man and its invasiveness for mice.

Despite the unusual micro-organism, the clinical course and the changes observed at autopsy were strikingly similar to those observed in cases of the common form of subacute bacterial endocarditis due to *Str. viridans*.

A comparison of the spirillum causing the subacute endocarditis in Lamb and Paton's case with the spirillum in the case presented here reveals striking differences in their biologic and cultural characteristics, as well as in their serologic effects in man.

Mount Sinai Hospital



# SALMONELLA CHOLERAE SUIIS MENINGITIS

## REPORT OF A CASE AND REVIEW OF THE LITERATURE ON SALMONELLA MENINGITIS

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In contradistinction to typhoid, the present day knowledge of paratyphoid infections of man is as yet incomplete, although important advances in this field have been made during the last few years. The identification of the various members of the *Salmonella* group presents difficulties far greater than those encountered in the recognition of the typhoid bacillus. The genus *Salmonella* is comprised of many different species and types. As a matter of fact, more than one hundred species have been described in the past as pathogens for human beings or animals or both. Special diagnostic antiserums are required to establish species or type identity. To add to the difficulty, the members of the *Salmonella* group are responsible for a variety of clinical syndromes. The diseases may be classified conveniently into three large groups: (1) paratyphoid, (2) gastroenteritis and (3) pyogenic infections. To the latter group belong such syndromes as septicemia, peritonitis, osteomyelitis, pharyngitis, otitis, abscesses, empyema, pyelitis, arthritis, cholecystitis, appendicitis, meningitis and others.

Purulent meningitis caused by members of the *Salmonella* group is not a common disease, although it is not so rare as is often believed. In 1940 Guerra, Peluffo and Aleppo,<sup>1</sup> in an excellent article, reviewed the literature on *Salmonella* meningitis. They collected 56 cases. Since that time additional cases have been reported. *Salmonella cholerae suis* accounts for only a small fraction of meningitis, although this particular organism is not uncommonly found as the cause of other diseases. Only 3 definitely established and well described cases of *S. cholerae suis* meningitis could be found in the literature. It was decided therefore to present the clinical, bacteriologic and immunologic observations of such a case and review the status of the *Salmonella*

meningitis problem with particular reference to the incidence of the various species in this malady.

### REPORT OF CASE

P. T., a white girl 3 years and 11 months of age, was admitted to the Children's Hospital (service of Dr. Norman C. Bender) on Sept. 22, 1943. The history revealed that the child was delivered instrumentally after seventy-two hours of labor. The birth weight was 8 pounds 8 ounces (3,856 Gm.). After birth extreme hydrocephalus developed, and the child had been blind. She sat alone at 12 months, walked at 30 months and talked at 2 years of age. Her mental development was retarded. There was no history of diarrhea or of other illness of consequence.

The physical examination on admission revealed the following facts. The child screamed almost continuously and appeared to be delirious. The temperature was 103 F., the pulse rate was 140 per minute and the respiratory rate 40 per minute. The head was extremely large. Its circumference was 25.5 inches (64.8 cm.) and that of the chest 21.5 inches (54.6 cm.). The anterior fontanel was closed. Nystagmus was present. The pupils were constricted and reacted only sluggishly to light. There was definite rigidity of the neck. The pharynx was slightly injected. The spleen and liver apparently were not enlarged. The Kernig sign was positive bilaterally, the Babinski sign was absent, and the deep reflexes were normal. There were no petechiae present. Roentgen ray examination of the chest revealed no abnormal conditions.

A culture of blood showed the presence of a paratyphoid bacillus. Its characteristics will be described later.

Examination of the blood showed a hemoglobin content of 12 Gm. and 3,700,000 red cells and 10,500 white cells per cubic millimeter, of which 54 per cent were polymorphonuclear cells, 40 per cent juvenile cells and 6 per cent lymphocytes.

A lumbar puncture was done on the day of admission. Approximately 20 cc. of slightly cloudy fluid was obtained. The pressure was greatly increased (above 500 mm. of water). This spinal fluid contained 119 leukocytes per cubic millimeter, of which 92 per cent were polymorphonuclear cells and 8 per cent lymphocytes. Globulin was present, and dextrose was absent. The microscopic examination revealed the presence of numerous gram-negative bacilli, subsequently identified as paratyphoid organisms. A second lumbar puncture was performed on the same day. The number of leukocytes had increased to 1,620 per cubic millimeter, dextrose was still absent, and globulin was present. The spinal fluid contained many gram-negative bacilli.

Examination of the feces failed to reveal paratyphoid bacilli, in spite of the fact that five different culture

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1 Guerra, A. R., Peluffo, E., and Aleppo, P. L. Localizaciones extraintestinales, en el niño, de las bacterias productoras de enteritis infantiles, in Bonaba, J., and others. Estudios sobre la etiología infecciosa de las diarreas infantiles, Montevideo, Editorial Medica J. Garcia Morales, 1940, pp. 91-130.

mediums (Endo, MacConkey, SS, desoxycholate-citrate and bismuth sulfite agar) were used

The serum of the patient was examined for the presence of specific agglutinins. The strain isolated from the spinal fluid was used as the antigen. Agglutinins were not present in dilutions of serum ranging from 1:10 to 1:1,000.

Sulfadiazine was given, 2 Gm immediately after admission and 1 Gm every four hours thereafter. In spite of this treatment, the child died the following day.

In order to determine the possible source of the infection, three members of the immediate family (father, mother and brother) were examined. Their feces did not contain paratyphoid bacilli, and agglutinins against the patient's strain could not be demonstrated in their serums.

The results of bacteriologic study were as follows. The blood culture contained innumerable colonies (per cubic centimeter) of gram-negative bacilli which had biochemical and antigenic characteristics identical with those of the strain isolated from the spinal fluid. The organism was motile and grew well on simple artificial

twenty years and to present the incidence of the different species and types of *Salmonella* organisms encountered in this malady. In addition to the data compiled from 56 cases by Guerra and associates,<sup>1</sup> 22 case reports have been collected. Indubitably, other cases have escaped detection. It seemed of no value to consider cases described many years ago, since no reliable information could be gained with respect to the incidence of the different *Salmonella* types. Furthermore, it must be admitted that in some of these cases a complete antigenic analysis of the respective strains was not carried out. Nevertheless, the figures shown in table 1 give an approximate picture of the incidence in meningitis of the various types of organisms of the paratyphoid group. There are several facts worthy of comment. In the first place, it may be seen that twelve different

TABLE 1—Incidence of Types of *Salmonella* in Meningitis

Group	Type or Species	Synonym of Species	Number of Cases of Meningitis	References
A	<i>S. paratyphi</i>		0	
B	<i>S. schottmuelleri</i>	<i>S. paratyphi</i> B	8	Patterson, <sup>11</sup> Schmidt, <sup>14</sup> Jundell, <sup>15</sup> Leenhardt et al., <sup>23</sup> Caselli and Teohalido, <sup>24</sup> Gordon, H., and Kennedy, J. A. <i>Am J Clin Path</i> 8: 170, 1938, Bahrenburg, J. H., and Ecker, E. E. <i>J Infect Dis</i> 60: 81, 1937
	<i>S. typhimurium</i>	<i>S. aertryke</i> <i>S. enteritidis</i> Breslau	17	Guerra et al. <sup>1</sup> Aballi et al. <sup>10</sup>
	<i>S. Sandiego</i>		1	Bray and Meredith <sup>10</sup>
C	<i>S. cholerae suis</i>	<i>S. supestifer</i>	5	Guerra et al. <sup>1</sup> , Boycott and McNeely, <sup>4</sup> Ravitch and Washington, <sup>6</sup> Kuttner and Zepp. <sup>6</sup>
D	<i>S. enteritidis</i>	<i>S. enteritidis</i> Gaertner	34	Guerra et al., <sup>1</sup> Crozier, <sup>13</sup> Wengeler, F. <i>Med Klin</i> 36: 1217, 1940, Opitz, <sup>21</sup> Hayasaka, <sup>25</sup> Meyer Robn, J. <i>Deutsche med Wchnschr</i> 66: 1193, 1940, Rieper, P. <i>Virchows Arch f path Anat</i> 289: 301, 1933
	<i>S. sp.</i> (Panama type)		1	Guerra et al. <sup>1</sup>
	<i>S. enteritidis</i> (variety Dublin)		5	Guerra et al. <sup>1</sup>
	<i>S. enteritidis</i> (variety Kiel)		1	Guerra et al. <sup>1</sup>
	<i>S. sp.</i> (Eastbourne type)		2	Guerra et al., <sup>1</sup> Valledor et al. <sup>26</sup>
	<i>S. enteritidis</i> (variety Jena)		3	Wengeler, F. <i>Med Klin</i> 36: 1217, 1940
E	<i>S. Sp.</i> (London type)		1	Willson and Gibson. <sup>18</sup>

mediums. It produced acid and gas from dextrose, maltose, mannitol, dulcitol, xylose, rhamnose and sorbitol. It failed to attack lactose, sucrose and salicin. The strain was tentatively identified as a member of the *Salmonella* group and was sent for further study to the New York *Salmonella* Center (Dr. Erich Seligmann, director). There it was identified as *S. cholerae suis*.

The postmortem examination was performed by Dr. Kornel L. Terplan. The significant conditions observed were the following:

Acute seropurulent meningitis. Very distinct, old hemorrhagic gliosis of the right cerebellar hemisphere, with firm membranous obliteration of the foramina of Luschka. Pronounced inner hydrocephalus. Massive recent suffusions in the leptomeninges in the right parieto-occipital area.

Acute, desquamative and moderately hemorrhagic enteritis, most severe in the duodenum and the lower portion of the ileum.

Scattered suffusions in the skin, especially of both extremities.

#### COMMENT

An attempt has been made to review cases of *Salmonella* meningitis described during the past

species or types have been encountered in the past as causative agents in this disease. These represent only a fraction of the species known to be pathogenic to man. It seems reasonable to assume, therefore, that in the future other species may be found in *Salmonella* meningitis. Secondly, it is interesting to note that not a single case of paratyphoid A bacillus meningitis is included in this group. However, Facatselli<sup>2</sup> mentioned by reference that this organism has been found in meningitis. Members of group B of the genus *Salmonella* account for 26, or one third, of all cases. Only 5 cases of meningitis were caused by *S. cholerae suis*, the sole representative of group C. More than half of all instances of *Salmonella* meningitis were due to members of group D. Group E is represented by *Salmonella sp.* (London type) in a single case.

2 Facatselli, N. Les manifestations méningées et les méningites d'origine éberthienne ou para-typhique, *Arch de med d enf* 42: 615-626 (Oct.) 1939.

Naturally, the question arises whether or not the incidence of these *Salmonella* types in meningitis is comparable to that in other *Salmonella* infections. Bornstein,<sup>3</sup> in his excellent review on the state of the *Salmonella* problem, reported on the type distribution among five hundred strains of *Salmonella* isolated from human beings in North America and Cuba during the years 1939 to 1941. Group A accounted for 2 per cent, group B for 47 per cent, group C for 38 per cent, group D for 7.5 per cent and group E for 5.5 per cent. It is not possible to compare the incidence of the different *Salmonella* types in these two series. Bornstein's figures were obtained over a three year period and included strains isolated in North America and Cuba only, whereas the figures for *Salmonella* meningitis cover a period of many years and include species recovered in Europe and South America as well. Nonetheless, it is impressive to note that group C is encountered in a lower percentage and group D in a higher percentage in meningitis than in *Salmonella* infections in general.

In this connection it is important to stress that all strains of *Salmonella* organisms encountered as causative agents in meningitis—and in other infections as well—should be adequately identified. Since many laboratories are not equipped to carry out the antigenic analysis of these strains, it seems advisable to send subcultures to *Salmonella* centers. Only then will it be possible to obtain an accurate picture of the incidence of the different *Salmonella* species in infections of man.

Among 78 cases of *Salmonella* meningitis reported in the literature, only 4 were due to *S. cholerae suis*, also referred to as *Salmonella* supestifer. An additional case has been reported in this study. Of the 4 cases previously published, only 2 are recorded in detail, 1 by Boycott and McNee<sup>4</sup> and the other by Ravitch and Washington.<sup>5</sup> The case of Kuttner and Zepp<sup>6</sup> is only briefly mentioned in their article. The patient was comatose on admission to the Baltimore City Hospital and died shortly afterward. No adequate history could be obtained. A diagnosis of chronic meningitis was made. The strain isolated from the spinal fluid

proved to be a monophasic supestifer, group 2. No data are available on the clinical aspects of the disease in the case of Materna and Januschke.<sup>7</sup> It is true that other cases of *S. cholerae suis* meningitis have been described in the literature. However, in the case of Lyon and Folsom,<sup>8</sup> for instance, this diagnosis was not adequately substantiated. The organism isolated by these authors was described as a bacillus producing acid and gas from certain carbohydrates. On the other hand, the subculture of this organism was identified at the Harriet Lane Home and at the National Institute of Health as an atypical influenza bacillus. This discrepancy in the results is difficult to explain unless one assumes that two different microorganisms were involved. If this is the case, either one of the organisms was a contaminant or the patient was suffering from a mixed infection. But even if the gas-producing organism was actually the causative agent of the disease (as a primary incitant or secondary invader), one cannot accept this case as an instance of *S. supestifer* infection, since the strain was not adequately investigated serologically.

Furthermore, a number of cases of meningitis were described during and after World War I as having been caused by bacilli of the Glasser-Voldagsen group and by paratyphoid bacillus N (Erzindjan), respectively (Hesse,<sup>9</sup> Neukirch<sup>10</sup>). According to the Kauffmann-White scheme, Neukirch's *Bacillus* Erzindjan is either *Salmonella* paratyphi C, *Salmonella* moscow or *Salmonella* enteritidis. The Glasser bacillus is identical with *Salmonella* typhi suis, and the Voldagsen variety is its monophasic nonspecific variety (Bornstein, personal communication). At any rate, these cases cannot be considered as instances of *S. cholerae suis* meningitis.

The pertinent features of the 5 cases of *Salmonella* cholerae suis meningitis are summarized in table 2.

The diagnosis of this infection presents certain difficulties. In the case reported here the micro-

3 Bornstein, S. The State of the *Salmonella* Problem, *J. Immunol.* **46** 439-496 (June) 1943.

4 Boycott, J., and McNee, J. W. Human Infection with American Hog-Cholera Bacillus, *Lancet* **2** 741-742 (Sept. 26) 1936.

5 Ravitch, M. M., and Washington, J. A. Supestifer Septicemia and Meningitis Complicating Meningococcic Septicemia and Meningococcic Meningitis, *J. A. M. A.* **109** 1122-1123 (Oct. 2) 1937.

6 Kuttner, A. G., and Zepp, H. D. Paratyphoid-Like Fever in Children Due to the *Salmonella* Supestifer Group, *Bull. Johns Hopkins Hosp.* **51** 373-387 (Dec.) 1932.

7 Materna, A., and Januschke, E. Ein Beitrag zu der Frage der atologischen Beziehungen zwischen der bazillaren Schweinepest und dem Paratyphus B des Menschen, *Ztschr. f. Fleisch- u. Milchhyg.* **35** 298-300 (July 1) 1924-1925.

8 Lyon, G. M., and Folsom, T. G. Meningitis Due to *Salmonella* Supestifer. Case Report, *West Virginia M. J.* **37** 249-255 (June) 1941.

9 Hesse, E. Zur Kenntnis der chirurgischen Komplikationen und Nachkrankheiten des Fleckfiebers, Rückfallfieber und des Paratyphus N (Erzindjan), einer Mischinfektion des Recurrens, *Arch. f. klin. Chir.* **128**: 739-814, 1924.

10 Neukirch, P. Ueber menschliche Erkrankungen durch Bazillen der Glässer-Voldagsengruppe in der Türkei, *Ztschr. f. Hyg. u. Infektionskr.* **85** 103-145, 1918.

scopic examination of the spinal fluid revealed numerous gram-negative bacilli. *Haemophilus influenzae* meningitis was therefore considered. Precipitation tests with the supernatant liquid of the spinal fluid and type-specific anti-*H. influenzae* serums yielded entirely negative results. Thus, it became unlikely that the patient was suffering from this particular infection. The cultural findings supported this assumption. The organism grew profusely in infusion broth and on Endo agar. Since there was no evidence that the organism produced acid from lactose (as indicated by the appearance of the colonies on Endo agar), a tentative diagnosis of typhoid or

the Widal test were positive six days preceding the appearance of the first signs of the meningeal infection. The patient observed by Smith<sup>12</sup> suffered from Gaertner bacillus enteritis for two weeks before meningitis developed.

In the majority of cases the portal of entry remains unknown. It is likely that the organism invades the blood stream from the intestinal tract or, in the opinion of the Uruguayan investigators, from the pharynx. In the case of my patient, examination of the feces failed to reveal the presence of paratyphoid bacilli. Moreover, the patient did not have diarrhea. On the other hand, it must be pointed out that the postmortem examination revealed definite inflammatory lesions in the intestinal tract. In cases with bacteremia the possibility should be considered that the intestinal lesions may be a sequela of, rather than the primary focus leading to, invasion of the blood stream.

With respect to the origin of the infection, it is possible either that *Salmonella* meningitis develops in carriers or that the organism originates from the outside. Crozier<sup>13</sup> reported an infection with *Salmonella* supposedly milk borne or water borne. In another instance the mother of a 6 week old infant who died from paratyphoid B bacillus meningitis harbored the identical micro-organism (Schmidt<sup>14</sup>). A similar experience was reported by Jundell<sup>15</sup>. An investigation was carried out to determine whether the infection of the patient reported here originated from members of the immediate family. Examination of the feces and blood serum of the child's father, mother and brother, however, yielded entirely negative results.

Of particular interest is the occurrence of epidemic outbreaks of *Salmonella* infections, including meningitis, in the newborn. Aballi and associates<sup>16</sup> reported the cases of 12 infants infected with *Salmonella aertrycke*. Apparently the central nervous system was involved in all cases. The spinal fluid was either xanthochromic, serous or frankly purulent. From the report it is difficult to determine how many of these infants actually suffered from *Salmonella* meningitis. However, it is probable that bacterial meningitis was present in 9 of these

TABLE 2—*Salmonella Cholerae Suis* Meningitis

	Boycott and McNee	Cases of Ravitch and Washington	Kuttner and Zepp	Materna and Januschke	Neter
Age (years)	35	4			4
Race		Negro			White
Sex	Female	Female			Female
Blood culture *	Positive	Positive			Positive
Feces culture *		Negative			Negative
Urine culture *		Negative			
Widal test †		Positive (1:2,560)			Negative
Previous diseases	None	Meningococcal meningitis and bacteremia			Hydrocephalus
Concomitant diseases	None	Meningococcal meningitis and bacteremia		Malaria	None
Therapy		Antimeningococcal serum			Sulfadiazine
Outcome	Fatal	Recovered	Fatal	Fatal	Fatal
Incidence of <i>Salmonella</i> infection among family					Stool cultures and Widal tests on father, mother and brother negative

\* Examined for presence of *S. cholerae suis*

† Examined for antibodies to *S. cholerae suis*

paratyphoid bacillus meningitis was made. Further biochemical and serologic examinations revealed that the bacillus belonged to the *Salmonella* group. It was identified as *S. cholerae suis*. The micro-organism isolated from the blood of the patient proved to be identical with that recovered from the spinal fluid.

The pathogenesis of *Salmonella* meningitis is not completely understood at the present time. In some of the cases the disease has been considered as primary, in others, as secondary. As far as the latter group is concerned, meningitis has been reported as a complication of paratyphoid, for example, by Patterson<sup>11</sup>. In Patterson's case the results of stool culture and of

11 Patterson, W. H. Paratyphoid B Meningitis. Two Cases Which Recovered, *Lancet* 1: 678-679 (June 6) 1942.

12 Smith, J. Gaertner Meningitis Complicating Gaertner Enteritis, *Lancet* 2: 705 (Oct. 1) 1921.

13 Crozier, T. H. Meningitis Due to Bact. Enteritidis (Gaertner), *Ulster M. J.* 7: 261-262 (Oct.) 1938.

14 Schmidt, B. Paratyphus-B-Meningitis bei einem Saugling, *Klin. Wchnschr.* 17: 303-304 (Feb. 26) 1938.

15 Jundell, I. A Case of Paratyphoid Meningitis, *Acta paediat.* 14: 229-231, 1932.

16 Aballi, A. A., Falcon, S., Sala Panisello, F., Curbelo, A., and Martinez Cruz, J. A. Salmonelosis del recién nacido, *Bol. Soc. cubana de pediat.* 9: 123-160 (April) 1937.

patients Guthrie and Montgomery<sup>17</sup> reported an epidemic outbreak of *Salmonella enteritis*. In all, 28 cases were observed. Of these, 11 were cases of purulent meningitis. The majority of these *Salmonella* infections occurred in a nursery of a maternity hospital, the infection in all likelihood was milk borne. The source of the epidemic could not be traced. One additional case of purulent meningitis caused by *S. enteritidis*, variety Dublin, was observed by these authors.

The Widal test is of limited value in the diagnosis of *Salmonella meningitis*, at least as far as its early recognition is concerned. In the case here reported agglutinins were not present in the patient's serum, probably because of the short duration of the disease. In other instances, however, the Widal reaction became positive during the course of the illness, for example in the cases reported by Wilsdon and Gibson,<sup>18</sup> Patterson,<sup>11</sup> Ravitch and Washington<sup>5</sup> and others. It is interesting to note that in the case observed by Ravitch and Washington<sup>5</sup> the agglutinin titer was only 1:80 on the twenty-first day of the illness, it increased to 1:320 on the thirty-third day and to 1:2,560 on the forty-second day.

The question arises: Why do *Salmonella* organisms localize in the meninges of patients with *Salmonella bacteremia*? Although no definite answer can as yet be given, it is evident that in some cases at least certain conditions create a *locus minoris resistentiae*. In the case reported in this study, for instance, meningitis developed in a child who had been hydrocephalic since birth. A similar observation was made by Bray and Meredith<sup>19</sup>. Guthrie and Anderson,<sup>20</sup> and Opitz,<sup>21</sup> as well as Ravitch and Washington,<sup>5</sup> described cases in which paratyphoid bacillus meningitis complicated meningococcic meningitis.

Aside from the problem of the localization of the organism in the meninges, it seems likely that *Salmonella bacteremia* and meningitis develop in persons with diminished resistance, particularly after other infections. This aspect of the problem

has recently been discussed (Neter<sup>22</sup>). In the case of Leenhardt, Boucomont, Labraque-Bordenave and Barnay<sup>23</sup> paratyphoid B bacillus meningitis followed otitis media. Caselli and Teobaldo<sup>24</sup> observed a newly born child in whom an infection of the urinary tract, caused by *Bacillus coli*, preceded paratyphoid B bacillus meningitis. Finally, attention should be called to the observations of Hayasaka,<sup>25</sup> who reported on Gaertner bacillus meningitis developing in patients infected with malaria for therapeutic purposes. The patient of Materna and Januschke<sup>7</sup> with *S. supestifer* meningitis suffered also from malaria.

The prognosis of *Salmonella meningitis* is still poor. Only a few cases with recoveries have been reported in the literature, for example, by Ravitch and Washington,<sup>5</sup> Valledor, García Pérez and Pedrera,<sup>26</sup> Patterson,<sup>11</sup> Storey<sup>27</sup> and Katsampes and Bradford.<sup>28</sup> As far as *S. cholerae suis* meningitis is concerned, Ravitch and Washington<sup>5</sup> described the only instance in which recovery took place. Treatment with sulfadiazine proved to be ineffective in the case of *S. cholerae suis* meningitis and bacteremia presented here. Of course, no conclusions with respect to the efficacy of sulfonamide compounds can as yet be drawn, since recovery may occur without the use of chemotherapy (Ravitch and Washington<sup>5</sup>). Finally, it may be pointed out that the sulfonamide compounds are not equally effective toward all species and types of the genus *Salmonella*.

Dr. Erich Seligmann identified the organism, and Dr. Norman C. Bender supplied the clinical data of this case.

219 Bryant Street

22 Neter, E. *Salmonella Cholerae Suis* (Weldin) Bacteremia, *Am J Dis Child* **64**:255-261 (Aug) 1942.

23 Leenhardt, E., Boucomont, J., Labraque-Bordenave, and Barnay. Meningite à paratyphique B chez un nourrisson, *Arch Soc d sc méd et biol de Montpellier* **18** 94-99 (Feb) 1937.

24 Caselli, E. G., and Teobaldo, C. T. Meningitis a bacilo paratifico B en un lactante, *Arch argent de pediat* **10** 416-423 (Oct) 1939.

25 Hayasaka, C. Im Verlauf einer Malaria durch *Bacillus enteritidis* Gaertner entstandene Meningitis und Sepsis, *Tohoku J Exper Med* **21** 466-504 (Sept 22) 1933.

26 Valledor, T., García Pérez, E., and Pedrera, J. Meningitis purulenta a *Salmonella Eastbourne* en un lactante de tres meses, tratado con sulfadiazina. Evolucion curativa despues de una recaída, *Bol Soc cubana de pediat* **14** 413-429 (Aug) 1942.

27 Storey, W. E. Purulent Meningitis Complicating Paratyphoid Fever. Report of a Case with Recovery, *J M A Georgia* **12** 472-474 (Dec) 1938.

28 Katsampes, C. P., and Bradford, W. L. Recovery from *Salmonella* (Panama) Meningitis in an Infant Treated with Sulfapyridine, *J Pediat* **16**:79-85 (Jan) 1940.

17 Guthrie, K. J., and Montgomery, G. L. Infections with *Bacterium Enteritidis* in Infancy with the Triad of Enteritis, Cholecystitis and Meningitis, *J Path & Bact* **49** 393-409 (Sept) 1939.

18 Wilsdon, K. F., and Gibson, A. Meningitis Due to *Salmonella* London, *Lancet* **1** 665-666 (May 24) 1941.

19 Bray, W. E., and Meredith, J. M. Fatal *Salmonella* Intracranial Infection in an Infant, *J Lab & Clin Med* **28** 152-156 (Nov) 1942.

20 Guthrie, K. J., and Anderson, T. Double Infection of the Meninges with *Meningococcus* and Gaertner's *Bacillus*, *Brit M J* **1** 193-194 (Feb 8) 1941.

21 Opitz, H. Zwei Falle von Mischinfektion mit *Bacillus enteritidis* Gaertner. *Monatschr f Kinderh* **15** 383-388, 1919.



## Book Reviews

**Synopsis of Diseases of the Heart and Arteries**  
By George R. Herrmann, M.D. Third edition  
Price, \$5.00 Pp 516, with 103 text illustrations  
and 4 color plates St. Louis C. V. Mosby Company, 1944

This is the third edition of this book to appear in eight years, the first appearing in 1936. The author has made some changes in this edition. They consist essentially of dividing the data into more chapters for emphasis and the inclusion of four new chapters dealing with psychogenic disturbances associated with heart disease, essential hypertension and disturbances in blood pressure and general systemic types of heart disease.

Since the handbook is intended for the use of students, who are in need of "succinct outlines," the reviewer is impressed by certain aspects of the presentation which fail in these objectives. There is a great tendency for repetition, which is surely not intended for emphasis. For example, on page 437 are found the following statements concerning the histamine test: "In a few minutes there normally develops a red spot which rises into a 1 cm wheal surrounded by flares 2 cm in diameter." "Within five minutes, in the presence of normal adequate superficial circulation, a 1 cm wheal surrounded by a 2 cm flare should develop." On page 73 is presented a photograph of a Boullitte oscillometer, and on page 433 is presented another photograph of the same instrument, in this instance in place on a leg. This seems unnecessarily repetitious when either illustration would suffice, and two photographs certainly suggest too much importance for an instrument of almost questionable value. On page 443 the author states that "Nicotinic acid and histamine base may be of benefit." One wonders the exact meaning of the vague term "histamine base." On page 435 the author states, in writing on a vasomotor test: "A positive reaction indicates that the coolness of a part was the result of a circulatory disturbance of spastic origin. If, on the other hand, there is no rise under these conditions, the low skin temperature must be the result of decreased peripheral circulation of an organic, anatomic, obstructive type of obliterative arterial disease." Such a statement is vague, suggesting that organic anatomic disease may not be associated with spastic and obstructive disease.

Periarteritis nodosa is included among the peripheral vascular diseases, while scleroderma, lupus erythematosus disseminatus, and dermatomyositis are not included. Periarteritis is no more a peripheral vascular disease than the diseases listed. The section on peripheral vascular diseases in general is presented too much from the surgical point of view. In fact, that section of the book is not presented very well as a whole, certainly not as well as the chapters on heart disease.

A considerable number of data, with detailed tables, are presented on the Schneider test for cardiovascular efficiency. Even though it is used by the military services, it is well known to be far from perfect. It would appear to be in order for one to deemphasize or at least present the subject with a critical attitude when writing a brief handbook for such medically im-

mature minds as possessed by medical students. When they enter the military services as medical officers they can learn the test in a matter of minutes should it be necessary.

The emphasis given the "cold pressor" test as an index of the hypertensive diathesis seems to be unwarranted by the generally accepted ideas and experiences concerning its value. Only a treatise on hypertension should contain very much detailed discussion on the subject at this stage of its evaluation.

On page 72 there is a section on the oscillometer which leaves the impression that all oscillometers are shaped and constructed like the Boullitte oscillometer, which, of course, is untrue, even though most of them are fashioned after the Pachon oscillometer. Incidentally, the author speaks of an "aneroid" to which the needle is connected. Obviously, such a use of the term aneroid is incorrect, as the word is an adjective. Apparently the author is referring to the bellows within the housing of the aneroid oscillometer. The author apparently feels (page 72) that the oscillometer measures the mean blood pressure. It is well to point out that there is no oscillometer yet available that will measure the mean blood pressure. Such claims have been made, usually with reservations, but they are not correct. Such an instrument would have many applications if it were available.

To electrocardiography is assigned 45 pages. Obviously, it is impossible to present this subject in such a concise form. Like many other authors, the attempt is made to do this, but is followed by the usual failure. Patterns are presented for the student to memorize, without any explanations of the mechanism which is responsible for the abnormalities. This is an error. Medical students should learn the reasons for and the mechanisms concerned. A good philosophic dissertation on the clinical applications and limitations of the electrocardiograph, with illustrations, is in order in a handbook of this sort. In other words, the subject should be presented thoroughly from a basic point of view to medical students if the book is intended for source of study, or not at all. As previously stated, the author perpetuates an error found in all one volume books on heart disease and has failed to clarify a common deficiency of monographs on heart disease.

There are other examples of weakness in the handbook. It is impossible to discuss each one. The presentation of bundle branch block from the point of view of the medical student is certainly vague and inadequate. This would be particularly true if a person should be confronted with the subject for the first time and seek information in the handbook. Another example is the list of the "Unquestionable evidences of heart disease," presented on page 466, which does not include a definite pericardial friction rub as a sign of heart disease.

Although the handbook has reached a third edition, to the surprise of the reviewer, it cannot be heartily recommended. Furthermore, and unfortunately for the lazy or busy student, cardiovascular disease and its management cannot be effectively presented in a synopsis as one might present a literary classic. Misinterpretation due to excessive brevity may lead to serious clinical consequences.



**Laboratory Methods of the United States Army**  
Fifth edition Edited by James Stevens Simmons, B S, M D, Ph D, D P H, Sc D (Hon), Brigadier General, United States Army, Chief of the Preventive Medicine Service, Office of the Surgeon General, United States Army, Lecturer in Tropical Medicine, Army Medical School, and Cleon J Gentzkow, M D, Ph D, Colonel, Medical Corps, United States Army, Commanding Officer, Deshon General Hospital, Butler Pennsylvania, formerly Chief of the Division of Chemistry and Physics, Army Medical School Approved by the Surgeon General of the United States Army Price \$7 50 Pp 823, with 103 engravings and 8 color plates Philadelphia Lea & Febiger, 1944

The medical officers who served in the division of infectious diseases in laboratories of the United States Army during the war of 1917-1918 may remember the first edition of "Laboratory Methods of the United States Army," published in 1918 This was a small pocket manual of 256 pages, a true vade mecum for the laboratory worker This fifth edition, of 823 pages, each of which is double the size of the page of the first edition, is a comprehensive laboratory manual It is dedicated to the memory of Dr George M Sternberg, who was Surgeon General of the United States Army during the last decade of the nineteenth century

The editors have enlisted the services of twenty-three contributors, all of them either officers in the army or closely related as consultants in special fields The book is divided into eleven parts as follows "Clinical Pathology," "Chemistry," "Mycology," "Bacteriology," "Rickettsiae and Filtrable Viruses," "Protozoology," "Helminthology," "Entomology," "Pathology," "Special Veterinary Laboratory Methods" and "Statistical Methods" Each of these parts has from one to twelve chapters, and usually several different authors have contributed to each part While the descriptions of technic are brief and the interpretations of necessity are much condensed, for the most part the procedures are adequate for the medical officer in a laboratory service Many chapters are followed by brief but adequate lists of references, which should stimulate further interest in special fields

Special mention may be made of the chapter on the chemical examination of water, sewage and industrial waste, not usually found in a laboratory manual This chapter, along with chapter 30, on the bacteriology of water and sewage, gives important methods for examination of these materials

There is a complete chapter of thirty-eight pages on toxicologic methods Part 3, on mycology, contains three chapters which, with the references, should prove very useful It may be hoped that in future editions there will be an expansion of this part of the book

Part 5 contains a chapter on rickettsias by Harry Plotz and a chapter on the filtrable viruses by John R Paul While both of these chapters are of necessity brief, they are up-to-date and contain real information on these important subjects

As may be expected, the chapters in the parts on protozoology and helminthology are complete and of real importance

Part 11, on statistical methods, is especially well done and should prove of use to the statistician

While this book is of particular interest to the army officer, it doubtless will be found to be a popular addition to the library of any physician interested in laboratory medicine

**Clinical Significance of the Blood in Tuberculosis**  
By Gullı Lindh Muller, M D Price, \$3 50 Pp 516  
New York The Commonwealth Fund, 1943

This book contains a critical review of the literature and detailed serial hematologic findings in 1,000 consecutive cases of pulmonary tuberculosis observed at the State Sanatorium at Rutland, Mass The values stressed are the red and white blood cell counts, differential count, hemoglobin content, hematocrit reading and sedimentation rate The various parts of the book include (1) the physiology of the blood-forming organs and the cellular response to the tubercle bacillus, (2) changes in the circulating blood in tuberculosis, (3) the sedimentation rate, (4) clinical and hematologic data as measures of constitutional reaction, (5) the effect of therapeutic methods, exercise and certain complications on the hematologic picture and (6) examination of the blood

The book is detailed enough to give the reader a comprehensive review of hematologic methods and interpretations, in which there have been such great advances in the last fifteen years Included are numerous tables and charts and a bibliography of 604 references It would have been helpful if the author had added summaries at the end of the chapters

Phthysiologists will find the volume of great assistance in making more extensive and intelligent use of hematologic data in the treatment of tuberculosis

**Synopsis of Neuropsychiatry** By Lowell S Selling, Sc M, M D, Ph D, Dr P H Price, \$5 00 Pp 473  
St Louis C V Mosby Company, 1944

The purpose of the author of this book appears to have been to collect the important contributions of the various schools of psychiatric nosology and therapy An eclectic approach of this type to a subject as important as psychiatry is worthy but difficult, unless one shows more unusual powers of discrimination than is suggested by the hodgepodge contained in these pages

The section on neurology offers little advantage in time saving over a standard text and has the disadvantage of any synopsis in that it handles inadequately the more complex syndromes The part on mental disorders inadequately describes the various forms of mental illness and the terminology used for them Instead the pet terminology reaction type of subdivisions, and so forth, of various contemporary psychiatrists receive rather more recognition than is necessary The frequent use of slang seems to this reviewer to have little place in a work of this type It is not apparent that the use of this pseudosemantic jargon increases the accuracy of the descriptions

**Terapeutica des los grandes sindromes digestivos.**  
Edited by C B Udaondo Pp 271, with 7 figures.  
Buenos Aires, 1943

This modest, paper-bound book gives an informal summary of the methods used at the National Public Dispensary for Digestive Diseases in the medical and surgical treatment of all varieties of gastrointestinal disorders Although it lacks an alphabetical index and attempts no critical appraisal of fundamental assumptions or statistical evaluation of results, the book is interesting as a readable account of prevailing theory and practice, for each of its eighteen chapters is written by a different specialist and numerous prescriptions are given, both medical and dietary

**Tropical Nursing A Handbook for Nurses and Others Going Abroad** By A L Gregg Second edition Price, \$3 00 Pp 185 New York Philosophical Library, 1944

The little book is valuable to persons bound for tropical zones for two reasons It gives excellent hints for the maintenance of health in the tropics and provides specific information about materials and equipment needed The larger portion is devoted to brief, clear descriptions of the numerous tropical diseases together with notes on treatment designed especially to meet the need of nurses and lay persons The material is well written, up-to-date and dependable The book is to be recommended for the purpose for which it was written, namely, as a small handbook useful to almost every one going to the tropics It would also serve well as a "Dispensary Handbook" in the tropics

**Die Blutersatzfrage im Felde** By Prof Dr A Fonio Price, 3 80 francs (Swiss) Pp 48 Berne, Switzerland Medizinischer Verlag Hans Huber, 1943

This booklet consists of a collection of five lectures on the use of blood substitutes on the battlefield written by the professor of surgery at the University of Berne, who reviews the whole subject with emphasis on the problem in the Swiss army With the exception of experiences of the German army in this field, most of the material discussed is well known to American physicians The absence of specific references detracts from the value of the lectures

**Vascular Responses in the Extremities of Man in Health and Disease** By David I Abramson Price, \$5 Pp 412, with 59 illustrations Chicago University of Chicago Press, 1944

In his preface the author states that this book is the result of a need for the collection between two covers

of the information on the vascular responses in the extremities which has accumulated in widely scattered journals He has accomplished his task in noteworthy fashion and has produced a comprehensive monograph, extensively documented, dealing with all phases of the subject Methods and clinical applications are thoroughly dealt with, and anatomic, physiologic and pharmacologic information is interpreted in its relation to disease The book should be valuable for reference

**Elimination Diets and the Patients' Allergies** By Albert H Rowe, M D Price, \$3 50 Pp 256 Philadelphia Lea & Febiger, 1944

This is the second edition of a well known and useful book The basic thesis of the author is that the use of cutaneous tests as a means of determining sensitizations to food is fallacious Certainly this is the general experience It follows, then, that other approaches are required to uncover the responsible foodstuffs The Rowe elimination diets have long been helpful in this regard Making allowance for a certain enthusiasm about the importance of foods in the production of symptoms, the book nevertheless is of value to all physicians and especially to allergists

**Symposium on Chronic Diseases In Medical Clinics of North America** Pp 291-524, with 44 figures Philadelphia and London W B Saunders Company, 1944

This volume contains eighteen articles on chronic diseases of various kinds Most of the authors are recognized authorities in their fields, and the general practitioner will be helped and stimulated by reading them There is, however, no organic relationship between the various articles, nor are they for the most part comprehensive There is a good deal of reiteration of common knowledge There are a number of tables and figures and an index

## CLINICOPATHOLOGIC STUDIES OF RENAL DAMAGE DUE TO SULFONAMIDE COMPOUNDS

A REPORT OF FOURTEEN CASES

FRANCIS D MURPHY, MD, JOSEPH F KUZMA, MD,  
THEODORE Z POLLEY, MD, AND JOHN GRILL, MD  
MILWAUKEE

It has become widely recognized that the kidney may be damaged in the course of therapy with sulfonamide compounds. Such renal complications may be classified roughly as follows: 1. Mechanical complications produced by masses of crystals of the sulfonamide compounds in the kidneys, pelves and ureters. These lead to obstructive lesions. This group may be further subdivided into (a) the extraneuphric, in which the concretions causing obstruction are within the pelves of the kidney or in the ureters, and (b) the intraneuphric, in which the concretions are in the kidney substance itself. 2. Toxic intraneuphric lesions without mechanical obstruction. These lesions occur within the kidney and are not associated with mechanical obstruction but may be attributed to the toxic effect of the sulfonamide compound on the parenchymal tissue. This class may be divided into three groups, which represent different phases of the same reaction and are not distinct divisions: (a) simple tubular degeneration, (b) necrotic tubular degeneration, and (c) glomerular changes. In some instances there may be evidence of obstruction and toxic parenchymal changes in the same kidney.

Shortly after the sulfonamide compounds came into general use, the mechanical or obstructive lesions were diagnosed and treated adequately. Nonobstructive toxic changes in the kidney were recognized a little later, and during the past few years a considerable number of such cases have been reported in the literature.<sup>1</sup> The combina-

tion forms have also been observed and commented on.<sup>2</sup> While the injuries of the kidneys caused by mechanical blocking of the urinary passages are the most common of all, the renal damage that occurs independently of obstruction is apt to be more serious. The reason for this is that the obstructive masses may be removed mechanically while the toxic injuries are not so amenable to treatment. Renal injury due to sulfonamide compounds requires prompt and early recognition of the damage, and this applies particularly to the toxic effects.

The purpose of this paper is to report the clinical and pathologic data for 14 patients, in all of whom renal damage developed after therapy with sulfonamide compounds.

### CLINICAL FEATURES

The observations on the 14 patients studied were made in the period from January 1939 to

(c) Lederer, M., and Rosenblatt, P. Death During Sulfathiazole Therapy, *ibid* **119** 8-18 (May 2) 1942. (d) Winsor, T., and Burch, G. E. Renal Complications Following Sulfathiazole Therapy, *ibid* **118** 1346-1353 (April 18) 1942. (e) Cutts, M., Burgess, A. M., and Chafee, F. H. Treatment of Lobar Pneumonia with Sulfathiazole and Sulfapyridine, *New England J Med* **223** 762-764 (Nov 7) 1940. (f) Finland, M., Peterson, O. L., and Goodwin, R. A., Jr. Sulfadiazine. Further Clinical Studies of Its Efficacy and Toxic Effects in 460 Patients, *Ann Int Med* **27** 920-934 (Dec) 1942. (g) Tragerman, L. J., and Goto, J. M. Fatal Reactions to Administration of Sulfonamide Drugs. Report of Five Cases, *J Lab & Clin Med* **25** 1163,1176 (Aug) 1940. (h) Eggleston, C., and Weiss, S. The Urinary Tract in Sulfonamide Therapy, *Am J M Sc* **202** 757-772 (Nov) 1941. (i) Bradiord, H. A., and Shaffer, J. H. Renal Changes in a Case of Sulfadiazine Anuria, *J A M A* **119** 316-318 (May 23) 1942. (j) Jeck, H. S., and Orkin, L. Toxic Renal Reactions Following the Use of Sulfadiazine, *J Urol* **49** 290-301 (Feb) 1943.

2 (a) Erganean, J. A., and Doval, J. H. Fatal Anuria Following Administration of Sulfonamides with Reference to Tubular Necrosis and Regeneration, *J Lab & Clin Med* **28** 808-812 (April) 1943. (b) Hellwig, C. A., and Reed, H. L. Fatal Anuria Following Sulfadiazine Therapy, *J A M A* **119** 561-563 (June 13) 1942. (c) Jeck and Orkin.<sup>11</sup>

Presented before the Sixteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov 5, 1943.

From the Department of Medicine, Marquette University School of Medicine, and the Medical Clinics and Department of Pathology, Milwaukee County General Hospital.

1 (a) Murphy, F. D., and Wood, W. D. Acute Nephritis and the Effect of the Sulfonamides on the Kidneys, *Ann Int Med* **18** 999-1005 (June) 1943. (b) Merkel, W. C., and Crawford, R. C. Pathologic Lesions Produced by Sulfathiazole. Report of Four Fatal Cases, *J A M A* **119** 770-776 (July 4) 1942.

September 1943 This clinical study will emphasize the following features (1) the disease for which the patient was treated, (2) the kind of sulfonamide compound and the amount of the drug given to each patient, (3) the largest, the average and the smallest total dose administered, (4) the first evidence of renal damage noted, (5) the subsequent course of the renal disorder, (6) the maximum blood levels of the drug at the time of renal injury and their varia-

tions, and, finally, (7) the cause of death and the postmortem diagnosis These data are summarized in the tables

Of the 14 patients, 4 were male and 10 were female The oldest was 64 years old, the youngest, 1 year The others ranged from 19 to 61 years of age Three of the 14 patients were given sulfonamide compounds for infections of the upper respiratory tract, 1 for erysipelas, 4 for lobar pneumonia, 1 for bronchopneumonia,

TABLE 1—*Clinical Data in Fourteen Cases of Renal Insufficiency Due to Intoxication with Sulfonamide Compounds*

Case No	Initials	Age, Yr	Sex	Occupation	Drug	Total Amount Given, Gm	Disease Treated	Maximum Blood Level of Sulfonamide Compound, Mg per 100 Cc	Urinary Findings
1	O G	56	F	Housewife	Sulfathiazole	18	Infection of upper respiratory tract		Albumin, +++ WBC, loaded RBC, many Casts, none Crystals, none
2	M S	51	F	Housewife	Sulfathiazole Sulfadiazine	22 6	Infection of upper respiratory tract, with acute streptococcal sore throat	16.6	Albumin, ++++ WBC, 2-5/h p f RBC, 25/h p f Casts, none Crystals, none
3	E T	25	F	Housewife	Sulfathiazole	15	Streptococcal septicemia	16.7	Albumin, + WBC, few RBC, few to many Casts, few, granular Crystals, none
4	A P	51	F	Inmate of infirmary	Sulfathiazole	15.5	Cystopyelitis	6.7	Albumin, +++ WBC, 8-10/h p f RBC, loaded Casts, many Crystals, none
5	A B	28	F	Housewife	Sulfanilamide	41	Septicemia secondary to septic endometritis	9.6	Albumin, none WBC, few RBC, none Casts, many Crystals, none
6	L S	44	M	Laborer	Sulfadiazine	38	Lobar pneumonia pulmonary abscess	11.0	Albumin, ++ WBC, many RBC, 20-25/h p f Casts, none Crystals, many
7	L D	45	F	Asylum inmate	Sulfanilamide	20	Erysipelas, chronic nephritis	15.0	Albumin, ++ WBC, loaded RBC, few Casts, granular coarse Crystals, 4-5/h p f
8	S M	61	M	Laborer	Sulfathiazole Sulfacetimide	34 26	Pneumonia of lower lobe of left lung	7.3	Albumin, ++ WBC, 3-4/h p f RBC, many Casts, none Crystals, many
9	F W	56	M	Laborer	Sulfadiazine	20	Lobar pneumonia	3.9	Albumin, ++ WBC, none RBC, many Casts, 1-2/h p f Crystals, many
10	M M	1	M		Sulfathiazole	0.65 (10 grains)	Gastroenteritis		Crystals, loaded
11	L V	64	F	Saleswoman	Sulfathiazole	8	Infection of upper respiratory tract	12.4	Albumin, ++++ WBC, 14-18/h p f RBC, many Casts, many, granular and hyaline Crystals, none
12	M S	19	F	Housewife	Sulfanilamide	10	Sepsis		Albumin, ++++ WBC, 7-10/h p f Casts, granular and hyaline
13	M S	19	F	Housewife	Sulfathiazole	39	Pneumonia	6.6	Albumin, +++ WBC, 1-2/h p f Casts, 1-4/h p f, granular Crystals, many
14	G S	38	F	Housewife	Sulfadiazine	34	Bronchial pneumonia	12.5	Albumin, + WBC, 1-2/h p f RBC, loaded Casts, few Crystals, many

1 for cystopyelitis, 3 for streptococcic septicemia and 1 for gastroenteritis (table 2). Of the sulfonamide compounds employed, sulfathiazole was the one of choice and was used in 7 cases. Sulfadiazine was given with sulfathiazole in 1 case, sulfadiazine alone in 2, sulfanilamide in 3 and sulfacetimide (acetylsulfanilamide) with

TABLE 2—Disease Treated and Sulfonamide Compound Used

Disease Treated	Number of Cases
Infection of upper respiratory tract	3
Gastroenteritis	1
Erysipelas	1
Lobar pneumonia	4
Bronchopneumonia	1
Cystopyelitis	1
Septicemia	3

Sulfonamide Compound Used	Number of Cases	Average Dose of Each Sulfonamide Compound, Gm
Sulfathiazole	7	15.8
Sulfathiazole (with sulfadiazine)	1	6.0
Sulfadiazine	2	31.0
Sulfanilamide	3	18.0
Sulfacetimide (with sulfathiazole)	1	26.0

Smallest single total dose used, 10 grains (0.65 Gm) of sulfathiazole

sulfathiazole in 1. The usual method of administration was followed for all patients, that is, 2 to 3 Gm of the drug was given at once and 1 Gm thereafter every four hours until it was discontinued for some reason. The largest total dose in any case was 41 Gm of sulfathiazole, and the smallest was 10 grains (0.65 Gm) of the same drug. The average total amount of sulfonamide compounds given before evidence of renal damage appeared was 20 Gm. Judging from these observations, the quantity of the drug used bears little or no relation to renal injury.

TABLE 3—Evidence of Renal Damage

Number of patients exhibiting renal damage before therapy	Albuminuria	5 cases
First evidence of renal damage after therapy was begun	Oliguria	12 cases
	Anuria	1 case
	Generalized edema	1 case
	Crystals	} with oliguria, 5 cases
	Red blood cells	
	Casts	
	Albumin	
	Red blood cells	} with oliguria, 7 cases
	Oasts	
	Albumin	} with anuria, 1 case
Debrls		
Blood levels of drug at onset of renal damage	Varied between 3.9 Mg per 100 Cc to 16.7 Mg per 100 Cc	

Five of the patients had mild albuminuria without other evidence of renal involvement before the drug was administered (table 3). This was considered no contraindication to the use of sulfonamide compounds as sometimes renal impairment not only does not become worse but clears during treatment with sulfon-

amide drugs.<sup>3</sup> Concerning the 14 patients under study, there was no correlation between the presence of albumin in the urine and the speed with which subsequent oliguria and anuria developed. The average time for the development of signs of serious renal damage was four days. Oliguria was the first evidence of severe renal insufficiency in 12 cases, anuria in 1 case and generalized edema in 1. In 5 cases, red blood cells, granular casts, albuminuria, and crystals of the sulfonamide compound were found associated with the oliguria. In 7 cases of oliguria, red cells, casts and albumin were present but crystals were absent. Retention of nitrogenous substances in the blood was observed in all but 4 cases. The nonprotein nitrogen content ranged from 60 to 218 mg per hundred cubic centimeters (table 4). The blood pressure was normal in all cases of this series, except in 1 in which glomerular involvement dominated the pathologic picture post mortem. In this case the blood pressure was abnormally high. In the other cases, there was no significant change of

TABLE 4—Nonprotein Nitrogen Content of the Blood

Evidence of Nitrogen Retention	Day of Onset of Nitrogen Retention After Therapy Was Begun	Ten Cases Nonprotein Nitrogen Levels, Mg per 100 Cc	Creatinine Levels, Mg per 100 Cc
6th		176.5, 200.0, 218.5	4.0, 4.0, 4.2
5th		60.0	1.5
5th		85.6, 92.3	2.3, 2.5
12th		85.6, 86.9	3.0
6th		75.9, 80.0	3.6, 4.8
2d		92.3	
4th		96.0, 128.4	3.19, 3.33
7th		62.8	
7th		135.0	
5th		62.4, 140.0	5.6

the blood pressure during the course of renal insufficiency.

The level of the sulfonamide compound in the blood was determined in all cases, but no correlation could be made between the height of the blood level and the type of damage sustained by the kidneys. As illustration, 1 patient with a blood level of the drug of 16.7 mg per hundred cubic centimeters exhibited nephrotoxic changes consisting of simple tubular degeneration, while in other cases, in which more severe damage was seen, the blood level was relatively much lower. Two patients showed the combination form of nephrotoxic and obstructive changes. In 1 the damage was caused by sulfathiazole and in the other by sulfadiazine.

3. Fishberg, A. M. The Use of Sulfonamides in Renal Insufficiency, *J. Mt. Sinai Hosp.* 8:509-513 (Jan-Feb) 1942. Williams, R. H., Longcope, W. T., and Janeway, G. A. The Use of Sulfanilamide in the Treatment of Acute Glomerulonephritis, *Am. J. Med. Sc.* 203:157-172 (Feb) 1942. Murphy and Wood.<sup>11</sup>

Of 14 patients, 5 died of uremia due to intoxication with the sulfonamide compound and 1 of uremia due to nephritis. One died of streptococcal septicemia, another, of septicemia secondary to septic endometritis, and 1, of sepsis with generalized peritonitis. Lobar pneumonia, in 1 case complicated by pulmonary abscess, accounted for 2 deaths and bronchopneumonia for 1. One patient died of portal cirrhosis associated with heart disease. The fourteenth patient (case 8 [S M]) survived after decapsulation of the kidney, but, as a section of the kidney was removed for biopsy, the case of this patient is incorporated with those of the 13 who died (table 5).

#### REPORT OF CASES

The study of our cases leads us to believe that there are three chief types of nephrotoxic damage of the renal parenchyma. Undoubtedly these are illustrative of different degrees of the same

TABLE 5—Cause of Death of 14 Patients Treated with Sulfonamide Compounds

Subject	Initial	Cause of Death
1	C G	Uremia due to sulfathiazole intoxication
2	M S	Uremia due to sulfathiazole intoxication
3	E T	Streptococcal septicemia
4	A G	Uremia due to sulfathiazole intoxication superimposed on intracapillary glomerular sclerosis of diabetes
5	A B	Septicemia secondary to septic endometritis
6	L S	Lobar pneumonia with pulmonary abscess
7	L D	Uremia due to nephritis
8	S M	Survived
9	I W	Lobar pneumonia
10	M M	Uremia due to sulfathiazole intoxication
11	L V	Lobar pneumonia with pulmonary abscess
12	M S	Sepsis with generalized peritonitis
13	M S	Bronchopneumonia
14	G S	Portal cirrhosis with obesity heart disease

pathologic process. Since the clinical features followed closely the same general pattern, 3 cases are given, each representing the clinical and pathologic phase peculiar to one of the types of nephrotoxic reaction found. Case 1 exemplifies the simple type of damage to the kidney due to toxic effects of sulfonamide compounds associated with obstruction. Case 2 represents the group characterized by extensive tubular degeneration with necrosis of the pyramids. The third case report is typical of the type in which extensive glomerular involvement is found in addition to widespread tubular injury.

**CASE 1**—L S, a man aged 44, entered the hospital complaining of hemoptysis and pain in the right side of the chest of five days' duration. The pain in the chest was accentuated by coughing, deep breathing and sneezing and was associated with fever, sweats, fatigue and weakness. The patient had had a loss of weight of 12 pounds (5.4 Kg.) in the past month.

Physical examination revealed a ruddy-faced, perspiring, well developed and well nourished white man, who appeared ill but in no respiratory distress. The

blood pressure was 110 systolic and 60 diastolic. The temperature was 102 F, the pulse rate 96 and the respiratory rate 24 per minute. The chest exhibited limited expansion, impaired percussion note, depressed breath sounds and a friction rub over the right lower portion anteriorly and posteriorly. Large moist rales were heard throughout the right side of the chest, predominantly at the right apex. A clinical impression of pneumonia of the lower lobe of the right lung was made.

The erythrocyte sedimentation rate was 122 mm in one hour and 126 mm in two hours.

The roentgenogram of the chest revealed a partial consolidation of the lower half of the right pulmonary field.

Urinalysis revealed nothing abnormal.

In addition to general supportive measures, the patient was given sulfadiazine, 2 Gm at once followed by 1 Gm every four hours with equal doses of sodium bicarbonate. He continued to have a temperature ranging between 100 and 102 F. Sulfadiazine was tolerated well, and the complaints were minimal except for that of a productive cough. The sulfadiazine level three days after his entry was 102 mg per hundred cubic centimeters. The urine on repeated microscopic examinations revealed no crystals, red cells or white cells.

On the ninth day after treatment was begun, the patient did not urinate. Catheterization at first yielded no urine, but later in the day approximately 1 ounce (30 cc) of urine containing numerous red and white blood cells was passed. The sulfadiazine level of the blood was 11 mg per hundred cubic centimeters. Determinations of blood chemistry showed a nonprotein nitrogen content of 62.8 mg and a creatinine content of 3 mg per hundred cubic centimeters. Up to this time the patient had received a total of 38 Gm of sulfadiazine.

Use of sulfadiazine was discontinued immediately. Fluids in the form of 5 per cent dextrose were given both orally and parenterally at the rate of 1,000 cc every four hours, but diuresis did not follow. A diagnosis of sulfadiazine obstruction was made. Cystoscopy was performed, and the washings from the bladder revealed numerous sulfadiazine crystals. Intravenous urograms indicated no definite abnormalities. A left posterior nephrostomy was done, but it was of little avail, though the patient did begin to void. Examination of the urine showed albumin (2 plus), occasional red blood cells and white blood cells and many sulfadiazine crystals. The course was retrograde, and the patient died approximately twenty-four hours after operation.

**Autopsy Report**—Conditions observed at autopsy were most significant in the liver, lungs and kidneys. The left kidney measured 18 by 9 by 7 cm, and weighed 550 Gm. The lower half of the organ was replaced by a large, lobulated, hemorrhagic, yellowish tumor. The capsule was loose. Throughout the cortical tissue there were numerous petechial hemorrhages and linear hemorrhagic streakings. Some of the pyramids were streaked with gritty, grayish, radiating lines extending toward the cortical tissue in a fanlike manner. The calices, pelvis and ureter contained a large amount of orange red sandlike concretions. At the ureteropelvic junction some of this material was firmly impacted, producing an obstruction and dilatation of the pelvis.

The right kidney weighed 330 Gm and similarly had a 2.5 cm yellowish red hemorrhagic tumor at the lower pole. The width of the cortex measured



12 mm. The gross observations were essentially the same as those of the left kidney. The proximal third of the ureter was completely obstructed by an impacted mass of concretions. The perirenal and hilar tissues of both kidneys were edematous. Similar orange red concretions were found in the urinary bladder. Above the left ureteral orifice were two grayish yellow necrotic plaques. The mucous membrane of the entire kidney-urinary bladder tract was injected and granular.

Microscopic examination revealed a bilateral hypernephroma. The concretions corresponded in structure to acetylated sulfadiazine. Aside from this, the kidney substance exhibited considerable degenerative changes in the convoluted tubules. Many of the epithelial cells were without nuclei and were greatly swollen, granular and vacuolated. Other tubular epithelium was

The lungs showed both gross and microscopic evidence of lobar pneumonia in the stage of gray hepatization.

CASE 2—C. G., a 56 year old white woman, was admitted to the hospital in a state of semicoma. The patient, known to have diabetes with albuminuria, acquired an infection of the upper respiratory tract with bronchitis three days before entry, for which she was given sulfathiazole, 1 Gm every four hours up to the time of admittance. Two days before entry she became grossly confused, and a day before her admission to the hospital a definite oliguria developed.

Physical examination revealed an extremely obese white woman, 56 years of age, pallorous and jaundiced and with a uremic odor to the breath. She was restless and confused. The blood pressure was 118 systolic

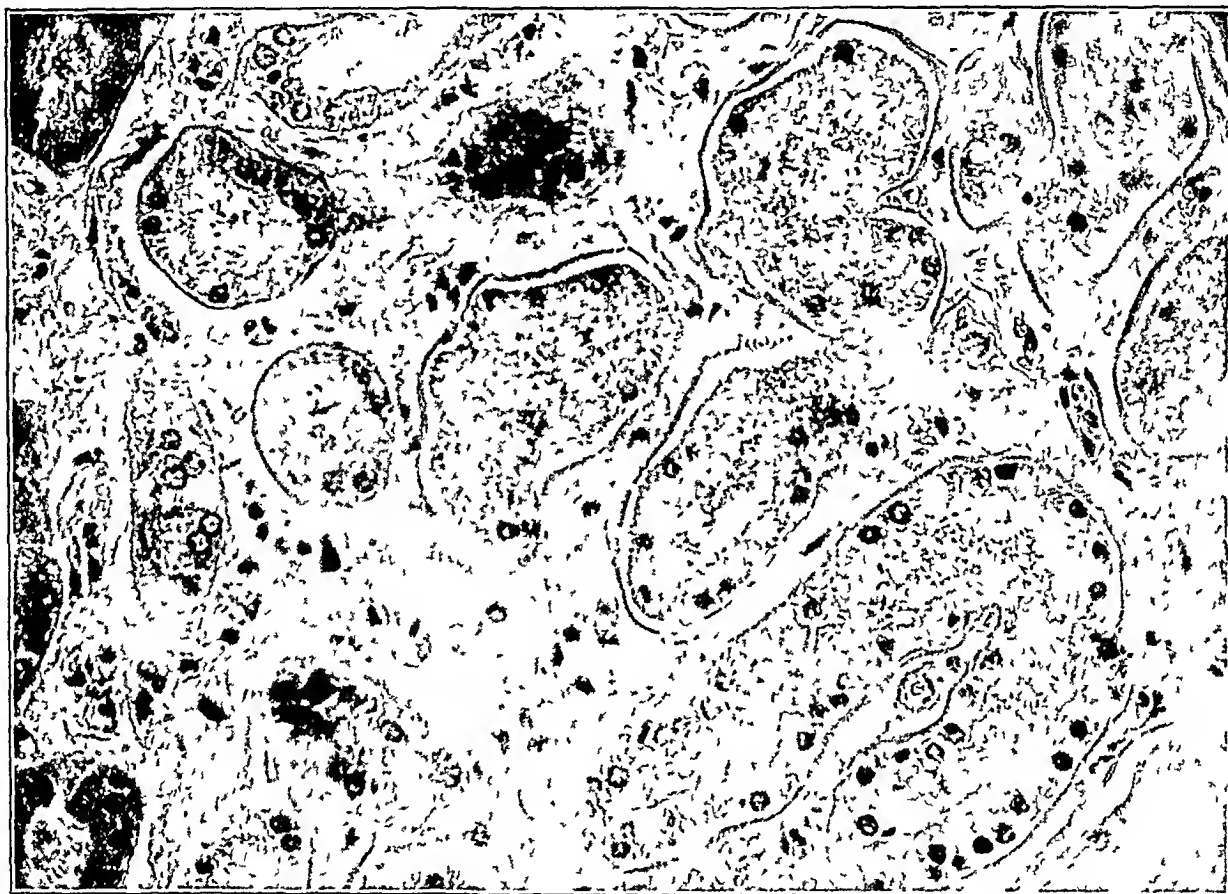


Fig 1—Tubular degeneration. The tubules are separated from each other by an edematous interstitial tissue. Many of the tubular epithelial cells have lost contact with the basement membrane and are greatly swollen, granular and vacuolated. The nuclei are absent in some cells and pyknotic in others. In some instances the tubular epithelium is condensed into a hyperchromatic mass or cells having the appearance of a giant cell. Hematoxylin and eosin, approximately 350 diameters.

desquamated (fig 1). The collecting tubules were filled with amorphous debris, consisting of cell detritus, proteins and sulfadiazine precipitates in noncrystalline form. Many glomeruli showed swollen tufts which filled out Bowman's space. All of the interstitial tissue was edematous and sparingly infiltrated by polymorphonuclear cells.

The liver weighed 2,440 Gm. Its capsule was tense and glistening, and the liver tissue was fatty, yellow and soft, with pronounced swelling of the lobular structure. Many of the cut surfaces were stippled with petechial hemorrhages. Microscopically the hepatic cord cells revealed swelling and granularity. Many were distended by large globules of fat. Occasionally areas of focal necrosis were seen. In such places the hepatic cells were replaced by an accumulation of inflammatory cells. Kupffer cells in general were swollen

and 64 diastolic. The temperature (rectal) was 98 F, the respiratory rate was 24 per minute and the pulse rate 92 per minute. A left apical systolic murmur was present, and the liver was palpable.

Examination of the urine revealed a 3 plus reaction for albumin, numerous white blood cells and 5 to 10 red blood cells per high power field. On entry, the red blood cell count was 2,850,000, with 7.5 Gm of hemoglobin, and the white blood cell count was 28,700, with 66 per cent stab forms and 24 per cent segmented forms. Chemical studies of the blood done at the same time showed a sugar content of 425 mg per hundred cubic centimeters, a nonprotein nitrogen content of 96 mg and a creatinine content of 3.19 mg.

Despite the giving of approximately 2,500 cc of fluid intravenously every day, the oliguria persisted. The nonprotein nitrogen content rose to 128.4 mg per hun-

dred cubic centimeters, and the carbon dioxide-combining power of the blood dropped to 42.8 volumes per cent. The patient grew steadily worse and became more confused, dyspneic and lethargic. She passed only 50 cc of urine during the terminal forty hours. On her fourth day in the hospital she died in a state of uremia.

*Autopsy Report*—At necropsy interesting gross changes were found in the kidneys. Both organs were greatly enlarged, having a combined weight of 600 Gm. As soon as the capsule was opened, the swollen, shiny, tense kidney substance bulged through. Between the capsule and the kidney substance a free fluid had accumulated. The cortical surface was glistening and smooth. Many petechial hemorrhages were visible on the surface. On section, the swollen, edematous tissue was seen to be mottled with large grayish and hemorrhagic areas. The cortex measured 10 to 12 mm and

cells desquamated into the lumen, forming intraluminal pseudo giant cells. Pus casts filled many of the tubules. Other tubules nearer the areas of reaction were more affected, and small areas of tissue were destroyed by foci of granuloma-like accumulations. These collections were composed of monocytic cells resembling epithelioid cells, numerous lymphocytes, polymorphonuclear cells and occasional eosinophils. At times these cells were seen about blood vessels and were accompanied by multinucleated giant cells (figs 3 and 4). Some of the vessels had closely applied giant cells completely surrounding the circumference of the vessel (fig 5). The glomeruli revealed arteriosclerotic changes of hyalinization of the tufts and afferent vessels.

The liver consistence was increased, and the surface appeared granular. The cut surface likewise presented a granular appearance due to the enlarged elevated lobules surrounded by depressed fibrous bands. The

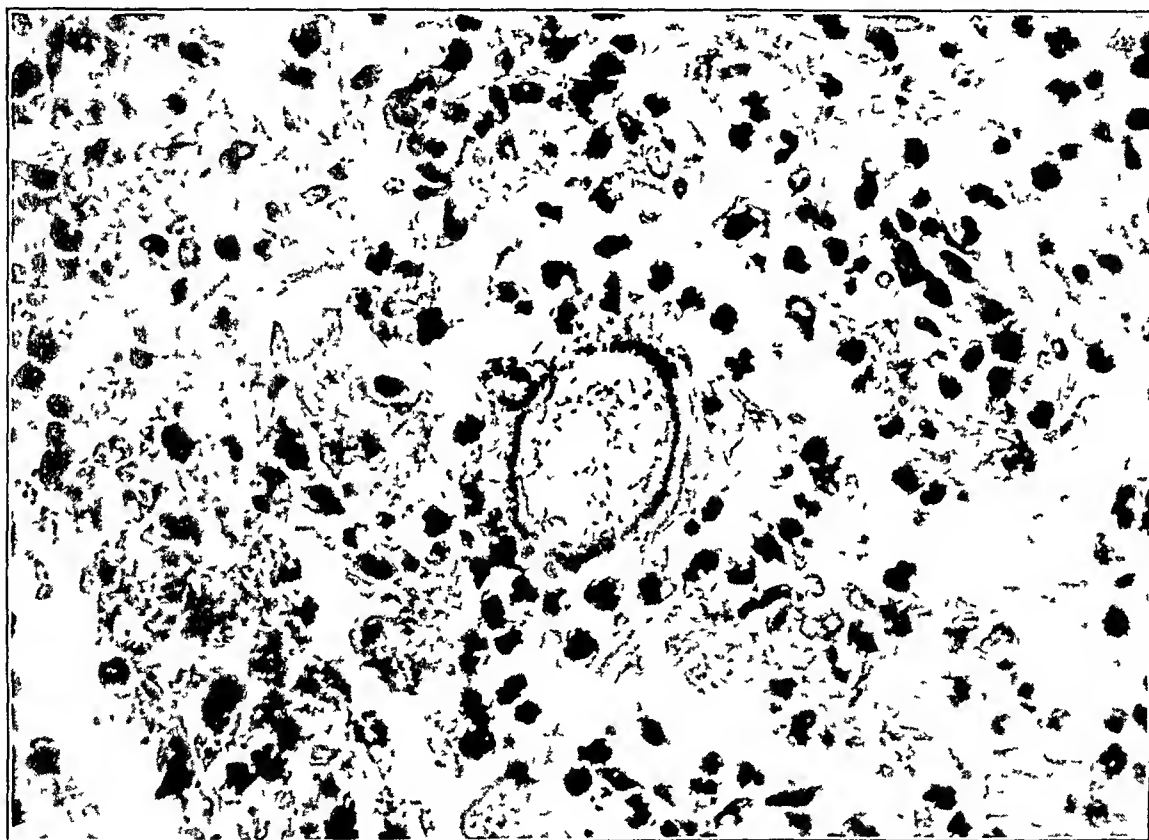


Fig 3—Perivascular distribution of the inflammatory cells. Many of the cells are polymorphonuclears, lymphocytes, plasma cells and epithelioid cells. The vessel wall itself is undergoing degeneration. Hematoxylin and eosin, approximately 700 diameters.

was streaked with numerous linear hemorrhages and petechiae. All of the pyramids were bulging, dull grayish and soft. The tissue of the pyramids showed complete necrosis but no evidence of any concretions (fig 2). All of the perirenal and hilar tissues were edematous.

Microscopic study of the kidney tissue revealed extensive necrosis of the pyramids. Such areas were represented by massive cellular disintegration. All tubular epithelium was lost, only the edematous, distorted interstitial tissue remained. The area between the viable cortical tissues and the necrotic pyramids was represented by a highly cellular reaction. Many of the cells of this zone were polymorphonuclear leukocytes. The viable tissue of the cortex and the columns of Bertini showed numerous hemorrhages and pronounced vascular engorgement. Many of the convoluted tubules were greatly swollen and the epithelial

conditions observed microscopically were those of portal cirrhosis with fatty infiltration and degeneration of the hepatic cells. In many areas small foci of necrosis were visible in the lobules. The cells in these foci were polymorphonuclear leukocytes, lymphocytes, monocytic cells, eosinophils and plasma cells. Pronounced swelling of the Kupfer cells was evident.

CASE 3—M. S., a 51 year old white woman, entered the hospital complaining of a sore throat of four days' duration. The day prior to her entry to the hospital her private physician gave her sulfathiazole, 1 Gm every four hours, with equal doses of sodium bicarbonate for an infection of the upper respiratory tract with acute streptococcal sore throat.

On entry to the hospital the patient had a temperature of 102 F, a pulse rate of 120 and a blood pressure of 114 systolic and 70 diastolic. On inspection she appeared toxic and febrile. The pupils were equal and reacted



Fig 2—Gross Kidney on hemisection The entire organ is greatly enlarged, glistening and streaked with hemorrhages Both the cortex and the pyramids are bulging The cortical tissue is wide, soft and edematous All pyramids are necrotic The gray-yellow necrosis involves most of the pyramid substance The mucous membrane of the calices and pelvis likewise is hemorrhagic



to light. The throat was of a beefy, dry color. There was no nuchal rigidity, and there were no palpable lymph nodes. The chest was essentially normal. The heart beat was rapid and regular, and a systolic murmur was heard at the base. The abdomen was distended, and there was some tenderness at both costo-vertebral angles. The upper and lower extremities plus the torso exhibited numerous erythematous papules, some with small areas of vesiculation and others with large blotches of erythema.

The patient was given sulfathiazole, 2 Gm every four hours, with equal doses of sodium bicarbonate. A study of the blood revealed a normal red cell count and a white cell count of 27,500, 21 per cent of which were stab forms, 61 per cent segmented forms and 18 per cent lymphocytes.

The urine on entry showed a 2 plus reaction for albumin and only 2 leukocytes per high power field.

seen. On the fifth hospital day oliguria was noted, and shortly afterward a drug rash developed. The use of sulfadiazine was discontinued, and fluids were forced parenterally as well as orally. The patient responded poorly.

By the eighth day in the hospital the patient had lapsed into a state of coma. The temperature (rectal) continued to spike between 101 and 104.5 F, and the oliguria became more pronounced. On the twelfth hospital day, the nonprotein nitrogen level had risen to 140 mg per hundred cubic centimeters, and the creatinine level was 5.6 mg. The coma became more profound, and the patient began to have edema of the lower extremities. The blood picture revealed a slowly progressive anemia, with the red blood cell count falling to 3,700,000 and the hemoglobin content to 60 per cent on the thirteenth hospital day. The urinary picture continued to show a 4 plus reaction for albu-

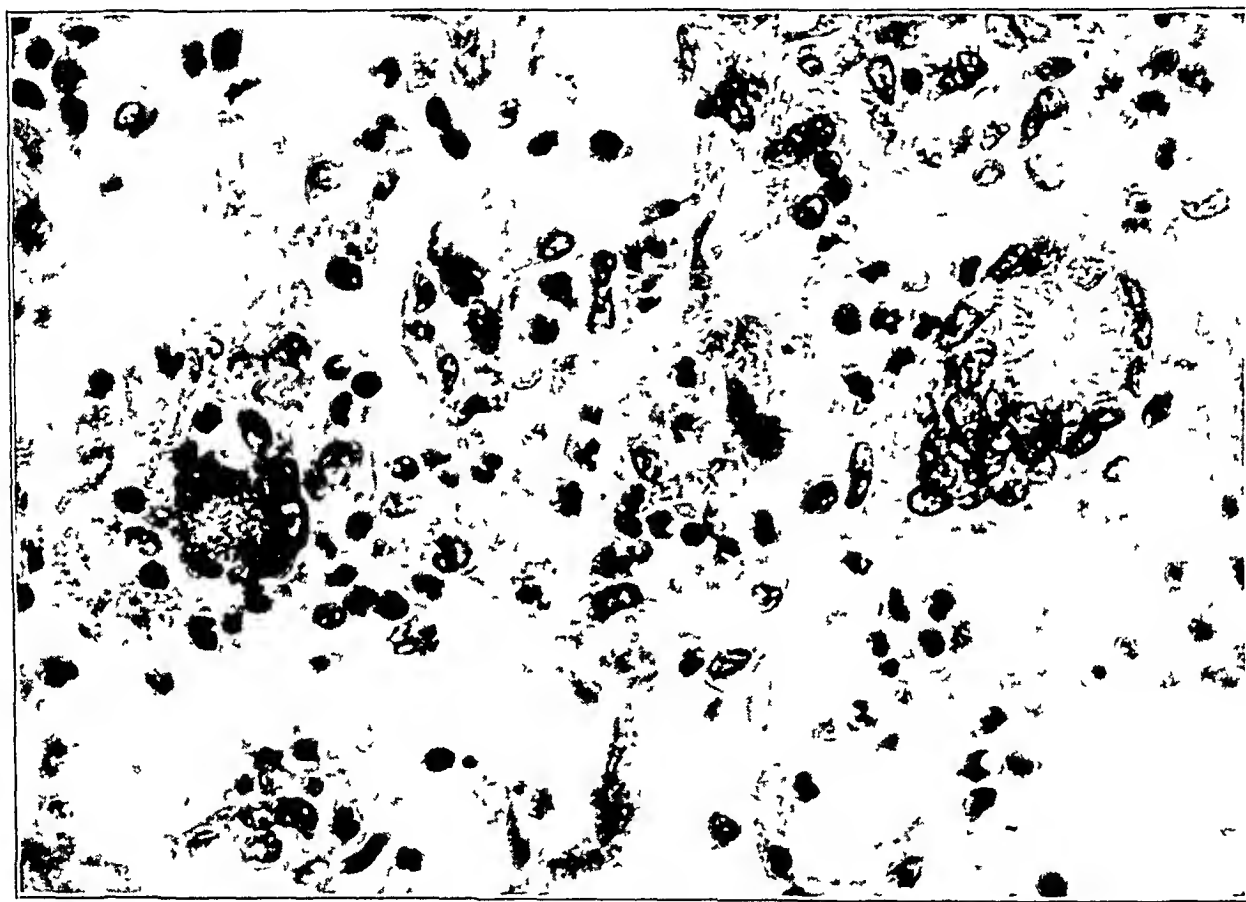


Fig 4—Giant cells in a granuloma-like focus. These giant cells are found in addition to the cellular Complement of figure 3. They arise from the epithelioid cells that may also be seen in the photograph. Hematoxylin and eosin, approximately 700 diameters.

Staphylococci and nonhemolytic streptococci were present in the culture of material from the throat.

After the first twenty-four hours, sulfathiazole was reduced to 1 Gm every six hours. On the patient's second day in the hospital the blood sulfathiazole level was 10.4 mg per hundred cubic centimeters. The urine showed a 4 plus reaction for albumin and approximately 25 red blood cells per high power field. On this day use of sulfathiazole was discontinued and administration of sulfadiazine was begun, 0.5 Gm every six hours. The temperature continued to rise and ranged between 102 and 105 F rectally. On the third hospital day, the level of sulfonamide compounds in the blood was 16.6 mg per hundred cubic centimeters. The urine continued to show a 4 plus reaction for albumin, and there was a great increase in the number of red cells. No crystals of sulfadiazine were

seen. Numerous red blood cells and white blood cells and many granular casts. In spite of alkalization, parenteral administration of fluids and general supportive measures, the patient died in a state of uremia on the thirteenth day after entry to the hospital.

**Autopsy Report**—The right kidney was swollen and weighed 260 Gm. The cortical surface was smooth and glistening and stippled with petechial hemorrhages. Throughout the congested, swollen, cut surface, there were yellowish gray pinpoint elevations. These were found in the columns of Bertini. The total cortex measured 10 to 12 mm in width. The pelvis and calices had a swollen, hemorrhagic mucous membrane.

The left kidney weighed 330 Gm. The substance was deeply congested and speckled with minute dots as seen in the right kidney. Many pyramids were grayish. Microscopic changes were those of moderately

advanced tubular degeneration involving particularly the convoluted tubules. Some of the collecting tubules, however, were filled with cellular debris and broken down polymorphonuclear cells. In the interstitial tissue small collections of polymorphonuclear cells, lymphocytes and plasma cells were found. Most pronounced changes, however, were limited to the glomeruli, which had advanced changes of hyalinization as described in intracapillary glomerulosclerosis of persons with diabetes who are past 40 years in age. In addition, many tufts were greatly distended by polymorphonuclear cells, lymphocytes and plasma cells. The epithelial cells were swollen and proliferating. Most glomeruli completely obliterated Bowman's space, and some had well developed epithelial crescents infiltrated by numerous polymorphonuclear cells (fig 6). In some instances the glomerular tufts blended almost imperceptibly with Bowman's capsule. The afferent arterioles were thickened and hyalinized.

The liver was enlarged, fatty and granular, weighing 2,300 Gm. The cut surface was of a tan color and speckled with petechial hemorrhages and some larger hemorrhagic foci. The lobules were indistinct. Microscopically the significant observations were focal cellular infiltrations of polymorphonuclears, lymphocytes and plasma cells in the lobules.

#### COMMENT

Of the numerous toxic complications caused by sulfonamide compounds, injury to the kidneys is the most serious. Safeguarding the kidneys becomes an important part of the treatment. While these complications are serious, they are comparatively uncommon when one considers the extensive use of the sulfonamide drugs. According to the classification of these complications, those belonging in the mechanical, extranephric group are not different from others encountered in the literature.<sup>4</sup> This is the most

common type of renal injury and responds best of all to therapeutic measures. When obstruction occurs within the kidney, a cure is not as easily accomplished, although retrograde lavage and discontinuation of the drug should always be done. Precipitation of the sulfonamide compound is the etiologic factor in these obstructions, precipitation should therefore be prevented so far as possible by the administration of adequate fluids and maintenance of an alkaline urine.

In this series of 14 cases, we have encountered a variety of renal changes due to the toxic effects of sulfonamide drugs on the renal parenchyma. In some instances the damage was the essential cause of death, while in others it was of a character serious enough to influence the course of the primary disease toward a fatal termination. Our observations substantiate the general impression that a diminishing output of urine in a patient taking any of the sulfonamide compounds is fair warning that renal injury has set in and that the use of the drug should be stopped promptly and restorative therapy started at once. The corollary to this impression has been that a diminishing oliguria and a satisfactory diuresis are sufficient evidence that the renal damage has been overcome and that a favorable outcome is forthcoming. This has met with contradiction in the work of Luetscher and Blackman.<sup>5</sup> They pointed out that in certain cases of damage to the kidneys by sulfonamide compounds diuresis may develop with a return to normal of the non-protein nitrogen of the blood but that the patient fails to recover. This is attributed to an excessive volume of urine without adequate excretion of salt. It is emphasized that the failure to replace this lost (saltless) water may lead to unfavorable consequences. Such a specific functional disturbance suggests, according to them, a corresponding specific renal lesion, which they found in the kidneys of 2 of their patients. The possible site of the specific renal injury was given

4 (a) Antopol, W., and Robinson, H. J. Pathologic and Histologic Changes Following Oral Administration of Sulfapyridine, *Arch Path* **29** 67-76 (Jan) 1940. (b) Knoll, A. F., and Cooper, F. B. Clinical Urolithiasis Medicamentosa Due to Sulfathiazole, *Urol & Cutan Rev* **44** 292-294 (May) 1940. (c) Snapper, I., Liu, S. H., Chung, H. L., Yu, T. F., and Sun, H. M. Hematuria Renal Colic and Acetylsulfapyridine Stone Formation Associated with Sulfapyridine Therapy, *Chinese M J* **56** 1-10 (July) 1939. (d) Pepper, D. S., and Horack, H. M. Crystalline Concretions in Renal Tubules Following Sulfathiazole Therapy. Widely Patent Foramen Ovale in Patient Aged 77, *Am J M Sc* **199** 674-679 (May) 1940. (e) Gross, P., Cooper, F. B., and Scott, R. E. Urolithiasis Medicamentosa, *Urol & Cutan Rev* **44** 205-209 (April) 1940. (f) Prien, E. L., Crabtree, E. G., and Frondel, C. Mechanism of Urinary Tract Obstruction in Sulfathiazole Therapy. Identification of Crystals in Tissue by Polarized Light, *J Urol* **46** 1020-1032 (Nov) 1941. (g) Loewenberg, S. A., Sloane, N. G., and Chodoff, P. Sulfathiazole Urinary Calculi in the Kidneys, Ureters and Bladder in the Absence of Marked Urinary Changes Following Sulfathiazole Therapy, *J A M A* **115** 2069-2071 (Dec 14) 1940. (h) Reinhold, J. G., Flippin, H. F., and Schwartz, L. Observations on the Pharmacology and Toxicology of Sulfathiazole in

*Man, Am J M Sc* **199** 393-401 (March) 1940. (i) Thompson, G. J., Herrell, W. E., and Brown, A. E. Anuria After Sulfadiazine Therapy, *Proc Staff Meet, Mayo Clin* **16** 609-612 (Sept 24) 1941. (j) Schulte, J. W., Shidler, F. P., and Niebauer, J. J. Acute Urinary Suppression Following Sulfadiazine Therapy, *J A M A* **119** 411-413 (May 30) 1942. (k) Keitzer, W. A., and Campbell, J. A. Renal Complications of Sulfadiazine, *ibid* **119** 701-703 (June 27) 1942. (l) Hall, W. H., and Spink, W. W. Sulfamerazine. Clinical Evaluation in One Hundred and Sixteen Cases, *ibid* **123** 126-131 (Sept 18) 1943. (m) Winsor and Burch<sup>1d</sup>. (n) Bradford and Shaffer<sup>11</sup>. (o) Jeck and Orkm<sup>13</sup>.

5 Luetscher, J. A., Jr., and Blackman, S. S., Jr. Severe Injury to Kidneys and Brain Following Sulfathiazole Administration, *Ann Int Med* **18** 741-756 (May) 1943.



as the intercalated segments of the distal convoluted tubules, the spiral portions of the proximal convoluted tubules and the ascending limb of Henle's loop. These authors added that in all of their cases it was not possible to correlate the retention of salt with the specific renal injury. However, their suggestion that every patient with oliguria due to a sulfonamide compound should be observed and treated with the electrolyte concentration of the blood in mind seems to us a valuable one. Although we did not study this group of patients with the hyperchloremic syndrome in mind, the occasional determinations done revealed that hyperchloremia existed in 1 case.

procedure brings relief is not entirely clear, but it may be possible that by reducing intranephric tension it helps restore normal renal function.

It has been shown experimentally and in man that the sulfonamide compounds may depress renal function. The literature also brings out that these drugs may go further and actually produce morphologic alterations of the renal tissue.<sup>8</sup> This observation has been confirmed by the experience reported in this study. Simple tubular degeneration is common to all kidneys damaged by sulfonamide compounds regardless of what other change may be present. Advanced tubular degeneration is seen in the more fulminating types of complications.<sup>9</sup> This may be

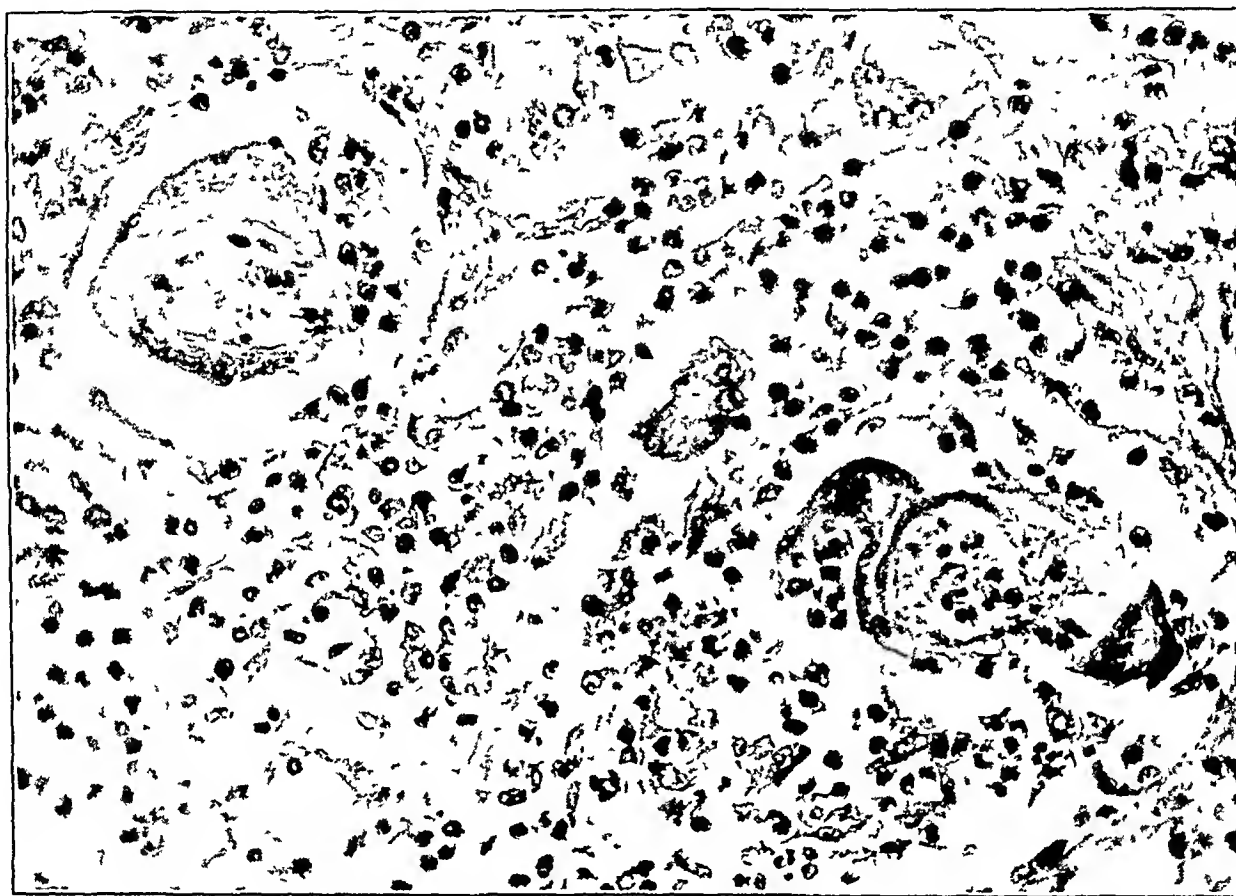


Fig 5—Cellular reaction showing the perivascular distribution of some of the giant cells. These are irregular multinucleated giant cells closely applied about the disintegrating vessel walls. Hematoxylin and eosin, approximately 350 diameters.

Decapsulation of the kidney has been advised for the treatment of resistant anuria due to intoxication with a sulfonamide compound. This operation was performed in 1 of our cases, with splendid results. Two other cases have been reported in the literature by Weinstein and Adams<sup>6</sup> and Wattenberg and Coleman.<sup>7</sup> Decapsulation in both of the cases was followed by favorable results. The mechanism by which this

6 Weinstein, M. L., and Adams, E. L. Sulfathiazole Anuria Cured by Decapsulation of the Kidneys, *Am J Surg* 60 105-111 (April) 1943.

7 Wattenberg, C. A., and Coleman, R. C., Jr. Sulfathiazole Toxic Nephrosis and Kidney Decapsulation. *Surgery* 14 570-573 (Oct) 1943.

8 (a) Finland, M., Strauss, E., and Peterson, O. L. Sulfadiazine. Therapeutic Evaluation and Toxic Effects on 446 Patients. *J A M A* 116 2641-2647 (June 14) 1941. (b) Ravid, J. M., and Chesner, C. Fatal Case of Hemolytic Anemia and Nephrotic Uremia Following Sulfapyridine Administration, *Am J M Sc* 199 380-385 (March) 1940. (c) Rake, G., van Dyke, H. B., and Corwin, W. C. Pathologic Changes Following Prolonged Administration of Sulfathiazole and Sulfapyridine, *ibid* 200 353-362 (Sept) 1940. (d) Merkel and Crawford.<sup>1b</sup> (e) Winsor and Burch.<sup>1d</sup> (f) Cutts, Burgess and Chafec.<sup>1c</sup> (g) Finland, Peterson and Goodwin.<sup>1e</sup> (h) Tragerman and Goto.<sup>1f</sup> (i) Eggleston and Weiss.<sup>1h</sup> (j) Bradford and Shaffer.<sup>1i</sup> (k) Erganian and Doval.<sup>2a</sup> (l) Hellwig and Reed.<sup>2b</sup> (m) Prien, Crabtree and Frondel.<sup>4f</sup>

(Footnotes continued on next page)

seen in conjunction with interstitial tissue reaction and necrosis. Since the sulfonamide drugs are actually toxic substances, it is not surprising that the tubular system of the kidney may be damaged. This is the usual expression of damage such as that brought about by poisoning with mercury. In some instances, however, there is not only degeneration but an active tissue reaction to the drug, exhibiting an intense inflammatory type of response. This is exemplified by our second case report. The reaction in such cases is probably an expression of severe idiosyncrasy on the part of the renal tissue to the drug. This is an important consideration in the observation of the inflammatory response

swelling of the glomerular tufts and congestion are the most common.<sup>9c</sup> Case 3, however, presents a far advanced reaction in the glomeruli. The severe swelling of the tufts, the obliteration of Bowman's spaces, the plugging of the tufts by polymorphonuclear cells and the proliferations of epithelial cells which are infiltrated with polymorphonuclear cells brings to mind the many changes of Bright's disease. However, in this case, with a clinical history of cystopyelitis, the histologic changes of intracapillary glomerulosclerosis of diabetes, the presence of plasma cells and eosinophils in the interstitial tissue and the clinical course and the age of the patient point away from the typical picture of Bright's disease.

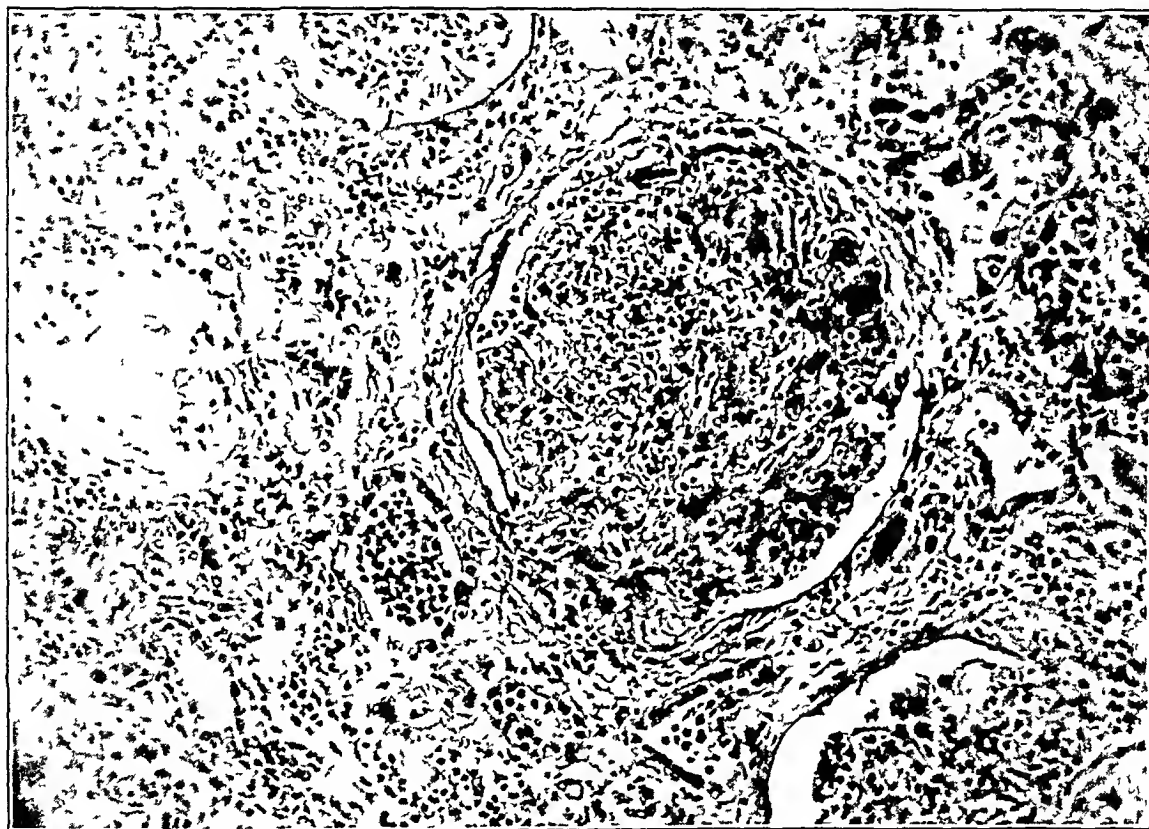


Fig 6—Glomerulus showing hyalinized thickening of some of the tufts and diffuse infiltration by polymorphonuclear cells. A loose crescent may be seen infiltrated by polymorphonuclears. Bowman's space is narrow and irregular. Hematoxylin and eosin, approximately 200 diameters.

outside the nephron, such as giant cells and the perivascular distribution of many of the granuloma-like cell accumulations. In this manner it may be true that it is actually an expression which is akin to periarteritis nodosa and other closely related lesions.

Glomerular changes are not encountered as frequently as tubular degeneration. Simple

On the other hand, it is impossible, in view of these conditions, to attribute all of the glomerular changes solely and unequivocally to the sulfonamide compounds. MacLeod<sup>10</sup> has called attention to the development of an atypical Bright's disease in 2 patients while receiving sulfapyridine for pneumonia. His patients recovered, but he expressed the belief that the drug was the responsible agent for the clinical picture resembling Bright's disease.

This study suggests that a close relationship may exist between hepatic damage and the

9 Maisel, B., McSwain, B., and Glenn, F. Lesions Produced with Sulfadiazine, *Proc Soc Exper Biol & Med* **49** 715-717 (April) 1942. Cabot Case 28501, New England J Med **227** 922-927 (Dec 10) 1942. Rottino, A., and La Rotonda, O. A Fatal Case of Urolithiasis Medicamentosa Caused by Sulfadiazine, *J Urol* **48** 310-317 (Sept) 1942. Merkel and Crawford<sup>1b</sup>

10 MacLeod, C. M. Chemotherapy of Pneumococcal Pneumonia, *J A M A* **113** 1405-1410 (Oct 7) 1939.

nephrotoxic complications. The changes in the liver may be independent of therapy with sulfonamide compounds or may be the result of such therapy. However, it may be, closely related hepatotoxic complications due to the sulfonamide compounds are occasionally encountered. Investigation of this is being carried on at present and will be reported at a future date.

#### SUMMARY

An opportunity presented itself to obtain clinical and pathologic data in 14 cases of renal insufficiency due to intoxication with sulfonamide compounds. Thirteen of the 14 patients died and were studied post mortem. Decapsulation of the kidney was done and a biopsy specimen taken in the case of 1 patient who recovered.

Most of the commonly used sulfonamide compounds were employed but sulfathiazole was the most commonly used one.

The primary disease under treatment was considered to play no part, or at any rate a small role, in causing the renal damage. Although 5 of the 14 patients treated had slight evidence of some renal involvement before therapy was begun, this was not considered a contraindication to the use of sulfonamide compounds, as these drugs have been used successfully in the treatment of acute nephritis.

The quantity of the sulfonamide compound administered and the drug level in the blood appeared to be unimportant in producing the renal damage. As much as 41 Gm and as little as 10 grains (0.6 Gm) were responsible for fatal renal injury.

In a few of our cases deposits of crystals of the drugs in the urinary tract causing some degree of mechanical obstruction were found associated with the nephrotoxic lesion, but this was not the rule, as in most of the cases reported the nephrotoxic lesion was independent of mechanical blocking.

Histologically there was simple tubular degeneration present in all the kidneys regardless of what other changes were present. Advanced tubular degeneration, necrosis of the tubular cells and intense inflammatory reaction outside the nephron in the surrounding tissues occurred in some cases. These various tubular lesions undoubtedly represent degrees in the severity of one process rather than different kinds of response. In 1 case advanced changes in the glomeruli are reported.

A correlation between the clinical features and the specific site for the renal tubular damage was not determined in this study.

# IMPORTANCE OF BRONCHOGRAPHY IN CASES OF UNRESOLVED PNEUMONIA

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The frequent demonstration of bronchiectasis by bronchographic studies in cases of unresolved pneumonia<sup>1</sup> has led to this study of 40 patients with bronchiectasis admitted to the station hospital, Fort Eustis, Va., from April 20, 1942 to July 20, 1943.<sup>2</sup>

It is the purpose of this paper not only to show the importance of bronchography in cases of unresolved pneumonia but also to demonstrate that in numerous cases pneumonitis secondary to bronchiectasis is misdiagnosed as primary atypical pneumonia. Atypical, or virus, pneumonia has become a disease of paramount importance in increasing the noneffective rate of military personnel during the past few years.<sup>3</sup> It has been noted at this hospital, both by physical and by roentgen examination, that in the average case atypical pneumonia resolves in about ten days, although the course may be prolonged for several months without any special complications. However, in some cases a condition which on the patient's admission was diagnosed clinically and roentgenographically as atypical pneumonia did not resolve completely and on further study, including bronchography, was found to be pneumonitis around a preexisting bronchiectasis. Ogilvie<sup>4</sup> stated that 36.8 per cent of his series of 68 patients with bronchiectasis demonstrated this syndrome. It is well known that recurrent pneumonitis is the most common complication of bronchiectasis, and any pneumonia which fails to resolve should be suspected of being bronchiectasis.<sup>5</sup> However, pul-

monary abscess, pulmonary tuberculosis and cancer of the lung must be considered. Bullowa<sup>6</sup> stated that bronchiectasis with consolidation surrounding the diseased bronchus may be mistaken for primary pneumonia and that pneumonia may be misdiagnosed bronchiectasis. In none of the cases of this series was bronchiectasis thought to be secondary to primary atypical pneumonia.



Fig 1 (case 4)—Flat plate roentgenogram of the chest, showing pneumonitis of the lower lobe of the left lung

1 Pneumonia in which the pulmonary signs fail to clear up in the usual period

2 The cooperation of the x-ray department, under Lieutenant T H Foust and Lieutenant R J Lutz Medical Corps, Army of the United States, made this study possible

3 Campbell, T A, Strong, P S, Grier, G S, and Lutz, R J Primary Atypical Pneumonia Report of Two Hundred Cases at Fort Eustis, Virginia, J A M A 122 723 (July 10) 1943

4 Ogilvie, A G Natural History of Bronchiectasis Clinical, Roentgenologic and Pathologic Study, Arch Int Med 68 395 (Sept) 1941

5 Lisa, J R, and Rosenblatt, M B Bronchiectasis, New York, Oxford University Press, 1943

Bronchiectasis stands second only to tuberculosis as the most common chronic disease of the lungs.<sup>7</sup> The routine roentgenograms of the chest of inductees have kept most men with pulmonary tuberculosis from being inducted into the Army, but many men with bronchiectasis are not detected, since a normal roentgenogram

6 Bullowa, J G M The Management of the Pneumonias, New York, Oxford University Press, 1939

7 Norris, G W, and Landis, H R M Diseases of the Chest, Philadelphia, W B Saunders Company, 1938

of the chest does not exclude bronchiectasis.<sup>8</sup> Patient 30 had a normal roentgenogram of the chest, but extensive saccular bronchiectasis was revealed by bronchographic study with iodized poppyseed oil (fig 4)

In this series of 40 patients, 9 were referred to the clinic for persons with diseases of the chest because of a history of chronic cough, hemoptysis or recurrent colds in the chest, while the remainder were admitted to the hospital with an initial diagnosis of primary atypical pneumonia



Fig 2 (case 8) —Tubular bronchiectasis of the lower lobe of the left lung

The symptoms on admission, in order of frequency, were cough, mucopurulent sputum with occasional blood streaking, substernal soreness, chills, fever and sweats. Examination revealed slight impairment of resonance, suppressed breath sounds, and fine, crackling and coarse rales in the lower lobe of one or both lungs. White blood cell counts showed slight leukocytosis but little increase in the polymorphonuclear neutrophils. The sputum did not settle into three layers in any case, and no organisms predominated, but those present were usually in the gram-positive coccus group. Clubbing of the fingers was not seen in any patient, although several men had long-standing symptoms and extensive disease. Roentgenograms demonstrated stringy and mottled densities in the lower lobes of the lungs, usually unilateral and radiating out from the hilus toward the dia-

phragm (fig 1). Lateral roentgenograms of the chest frequently revealed a pneumonic process behind the diaphragm or a cardiac shadow which could not be seen in the posterior-anterior exposure.

After four or five days the acute febrile stage usually subsided and the cough abated somewhat, with less sputum, while suppressed breath sounds and rales persisted or improved slightly. Follow-up roentgenograms of the chest were taken at seven to ten day intervals and showed little evidence of clearing.

Bronchographic studies were done in cases in which resolution failed to occur in four to six weeks, and iodized poppyseed oil was injected into both sides even when the pneumonic process was unilateral. Studies with iodized oil are contraindicated in the period of acute pneumonitis, since this procedure may produce an exacerbation of the acute process.



Fig 3 (case 4) —Fusiform and tubular bronchiectasis of the lower lobe of the left lung

#### TECHNIC OF BRONCHOGRAPHY

In preparation for the bronchographic study, the patient takes nothing by mouth after breakfast. At 11 a. m. he is given 3 grains (0.18 Gm.) of sodium amytal. At 1:30 p. m.  $\frac{1}{6}$  grain (0.01 Gm.) of morphine sulfate and  $\frac{1}{150}$  grain (0.4 mg.) of atropine sulfate are administered. Local anesthesia is induced with cocaine hydrochloride, a 2 per cent solution being sprayed into the pharynx and a 10 per cent solution being injected into the larynx with a laryngeal cannula. The

<sup>8</sup> Hedblom, C. A. Surg., Gynec. & Obst. 52:406, 1931

*Statistical Data*

Case	Age	Date of Broncho gram	Past History of Diseases of Chest	Diagnosis on Admission	Type of Bronchiectasis	Extent	Location	Comments
1 J M	27	4/20/42	None	At pneumonia R L L	Fusiform	Moderate	R L L, R M L	
2 W M	33	4/21/42	Chronic cough pneumonia 1926	Bronchiectasis	Fusiform	Moderate	R M L, L L L	
3 A R	27	4/27/42	Chronic cough	At pneumonia L L L	Fusiform	Moderate	L L L	
4 J C	28	4/28/42	None	At pneumonia L L L R U L	Fusiform	Extensive	L L L	
5 H W	36	7/ 1/42	Chronic cough	Bronchiectasis	Saccular	Moderate	L L L	
6 J D	26	7/ 7/42	Pneumonia 10 yr ago	At pneumonia L L L	Fusiform	Moderate	L L L	
7 W K	37	8/15/42	None	At pneumonia R L L, L L L	Fusiform	Mild	R L L, L L L	
8 G W	25	8/18/42	Worked in soap stone dust, cough 2 mo	Bronchiectasis	Tubular	Moderate	L L L	Pneumoconiosis patient admitted after severe hemoptysis
9 W M	28	8/21/42	Chronic cough	Bronchial asthma	Tubular	Moderate	L L L	
10 C S	40	8/26/42	None	At pneumonia R L L	Saccular	Moderate	R L L	
11 G T	27	8/31/42	Chronic cough for years	Bronchiectasis	Tubular	Moderate	L L L	Dementia precoc
12 J M	31	9/25/42	Chronic cough 2 yr, worse in past 2 mo	At pneumonia L L L	Fusiform	Mild	L L L	Secondary anemia
13 D D	24	9/29/42	None	At pneumonia R L L	Fusiform	Moderate	R L L, L L L	
14 C S	25	10/ 1/42	Pneumonia 5 yr ago chronic cough	Bronchiectasis	Fusiform	Moderate	R L L, L L L	Loss of weight, postnasal drip for 1 yr, secondary anemia
15 W G	35	10/30/42	Chronic cough	Bronchiectasis with pneumonitis	Fusiform	Mild	L L L	Abcessed teeth
16 J S	44	11/12/42	Chronic cough 15 yr	Bronchiectasis with pneumonitis	Tubular	Mild	L L L	Frequent hemoptysis, profuse sputum
17 W B	21	11/18/42	None	At pneumonia L L L	Tubular	Extensive	L L L	
18 G J	20	11/27/42	Pneumonia twice in childhood chronic cough	At pneumonia L L L	Fusiform	Moderate	R L L, L L L	Frequent colds in chest
19 W P	34	11/27/42	Pneumonia in childhood	At pneumonia bilateral	Tubular	Moderate	L L L	
20 A P	40	11/28/42	Chronic cough	Bronchiectasis with pneumonitis	Saccular	Extensive	L L L, R L L	
21 H S	20	1/ 6/43	None	At pneumonia L L L	Tubular	Extensive	L L L	
22 J R	20	3/ 3/43	Chronic cough	At pneumonia L L L	Tubular	Extensive	L L L	
23 C S	27	3/17/43	Chronic cough since childhood	At pneumonia L L L	Tubular	Moderate	L L L	Postnasal drip for 20 yr
24 F G	28	3/18/43	None	At pneumonia R L L	Tubular	Localized	R L L	
25 A G	34	4/ 5/43 5/12/43	None	At pneumonia, atelectasis	Tubular	Mild	L L L	Second broncho gram showed improvement
26 J H	20	3/23/43	None	At pneumonia L L L	Tubular	Moderate	L L L	
27 S W	32	4/ 9/43	Chronic cough for years	Chronic bronchitis	Fusiform	Localized	L L L	Second broncho gram 2 mo later showed improvement
28 R C	18	4/23/43	Chronic cough since pneumonia at 4	Lobar pneumonia	Saccular	Extensive	R L L	Prolonged convalescence from pneumonitis
29 G L	18	5/ 3/43	None	At pneumonia	Fusiform	Mild	R L L	Persistent signs of consolidation
30 C H	19	5/ 6/43	Cough since pneumonia 1941	At pneumonia	Saccular	Extensive	R L L	Marked puddling effect on broncho gram
31 A T	20	5/ 8/43	None	Acute bronchitis	Tubular	Mild	R L L	
32 D H	20	5/18/43	Chronic cough for years	At pneumonia R L L	Tubular	Moderate	R M L, R L L	
33 C M	21	5/22/43	None	At pneumonia R M L	Tubular	Moderate	R M L	
34 C S	31	5/28/43	Chronic cough, bronchopneumonia 2 yr ago	Bronchiectasis	Saccular	Localized	R L L	Frequent colds in chest and hemoptysis
35 C S	20	6/ 3/43	None	At pneumonia R L L, R M L	Fusiform	Extensive	R M L, R L L	
36 E M	21	6/10/43	Cough since pneumonia 1942	At pneumonia R L L	Tubular	Moderate	R M L, R L L	
37 R G	19	6/11/43	Frequent chest colds since childhood	At pneumonia R L L	Tubular	Moderate	R L L	
38 W L	27	6/23/43	Chronic cough since pneumonia ("flu") 1933	At pneumonia L L L	Tubular	Extensive	L L L	
39 E T	19	7/ 1/43	Chronic cough 2 yr	At pneumonia	Fusiform	Localized	R M L	
40 R M	19	7/20/43	Chronic cough since pneumonia 1942	At pneumonia L L L, R L L	Tubular	Moderate	L L L	



actual bronchographic examination is then carried out as follows

1 Using a soft rubber catheter, place the tip in the piriform sinus as shown under fluoroscopic examination in the lateral view

2 Inject iodized poppyseed oil after the patient has been placed in the desired position to outline a specific lobe

3 Under fluoroscopic control note well the flow of the oil through the bronchi out into the alveolar spaces

4 Take stereoscopic anterior-posterior and oblique films when both sides are outlined. If



Fig 4 (case 30)—Saccular bronchiectasis of the lower lobe of the right lung, with a puddling effect. The bronchogram of the lower lobe of the left lung is normal.

one side is being studied a lateral may be substituted for the oblique view.

Postural drainage should be instituted after the patient returns to the ward.

Although the age group was limited, it was found that the average age was  $26\frac{1}{2}$  years and that 17 patients were under 25 years, 17 between 25 and 35 and 6 over 35.

#### SUMMARY OF CLINICAL DATA

In summarizing the statistical data (presented in the accompanying table) it is found that the distribution of bronchiectasis was usually unilateral (30 cases) and most frequently involved the lower lobe of the left lung (20 cases, 50 per cent). The preponderance of left-sided disease

in instances of unilateral bronchiectasis is in accord with Ogilvie's<sup>4</sup> series. The lower lobe of the right lung was occasionally affected alone (8 cases, 20 per cent), while the middle lobe of the right lung rarely demonstrated the disease by itself (2 cases, 5 per cent). Bilateral distribution was noted in 6 cases (15 per cent), in 5 of these the lobes of both lungs were involved, while in the remaining case the middle lobe of the right lung and the lower lobe of the left were affected. In 4 cases (10 per cent) the diseased bronchi were limited to the middle and lower lobes of the right lung together. Farrell's<sup>9</sup> figures in 100 cases showed involvement of the left lung in 41 per cent, of the right lung in 23 per cent and of both lungs in 36 per cent. Fletcher<sup>10</sup> found a similar distribution in 100 cases, with the left lung involved in 43 per cent, the right lung in 25 per cent and both lungs in 32 per cent. It is interesting to note that none of the patients in whom disease of upper

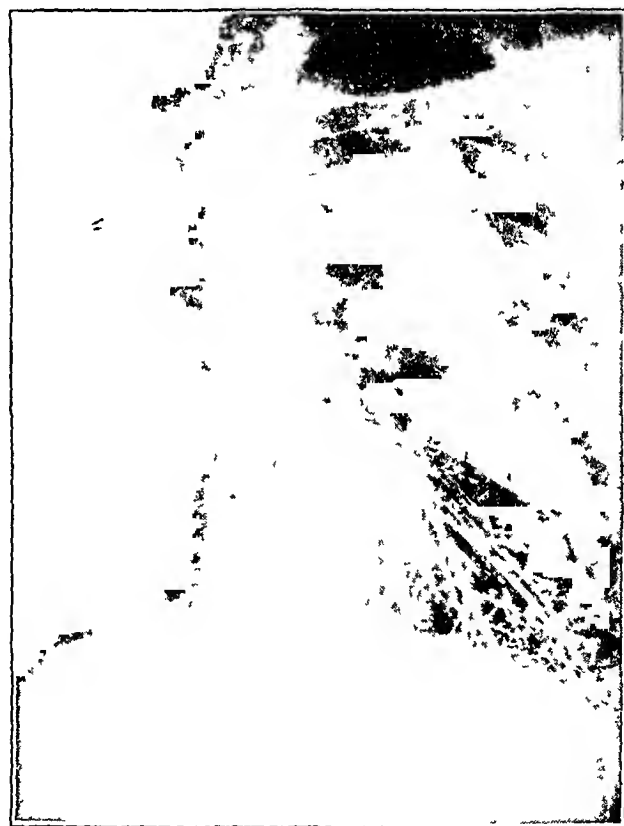


Fig 5—Bronchogram showing blunting of the bronchi and absence of alveolar filling, with no evidence of dilatation of the bronchi. This patient had some atelectasis of the lower lobe of the left lung.

lobes was suspected could be demonstrated to have bronchiectasis in the upper lobes.

Tubular (19 cases) and fusiform (15 cases) dilatations were the most frequent type of

9 Farrell, J. T., Jr. Importance of Early Diagnosis in Bronchiectasis. Clinical and Roentgenologic Study of One Hundred Cases, *J. A. M. A.* 106:92 (Jan 11) 1936.

10 Fletcher, E. J. *J. Thoracic Surg.* 4:461, 1935.

bronchiectasis demonstrated while the saccular form (6 cases) was seen rather infrequently (figs 2, 3 and 4)

According to Lisa and Rosenblatt<sup>6</sup> the size and extent of the dilatations have no direct relation to the severity of the disease. However, it is of interest to note that 9 patients in this series showed extensive bronchiectasis, 20 moderately severe and 7 mild, and only 4 had localized disease.

In 2 cases not included in this series a diagnosis of primary atypical pneumonia was made on the patient's admission and the course of the disease was similar to that described in this study. Bronchographic studies did not show dilatation of the bronchi but demonstrated atelectasis, as shown by absence of alveolar filling, blunting and crowding together of the bronchi (fig 5). Follow-up studies with iodized oil in six weeks revealed complete aeration of the atelectatic areas and normal bronchial trees. These 2 cases are mentioned because atelectasis without bronchial dilatation must not be confused with atelectatic bronchiectasis, since the former is reversible while the latter usually is not.<sup>4</sup>

Brennemann<sup>11</sup> stated that early diagnosis of atelectasis as a prebronchiectatic condition is important and that the condition can be cured by removal of the obstruction and bronchoscopic aspiration.

#### COMMENT

It has been found in this study that the differential diagnosis between primary atypical pneumonia and pneumonitis around bronchiectasis is difficult at the onset. A history of chronic cough,

especially following bronchopneumonia in childhood, hemoptysis, profuse sputum or frequent colds in the chest makes one suspicious of bronchiectasis, although in some cases the past history may be entirely without such elements. In the series under study, only 23 patients gave a history of chronic cough, and in 9 of these patients the cough developed after a previous attack of pneumonia.

The frequent diagnosis of this disease is brought out by the fact that during the fifteen months in which this study was made there was an average of 2.66 cases a month. This is significant when one considers that the patients were inducted into the Army as healthy young men.

The importance of bronchography in cases of unresolved pneumonia is demonstrated by the fact that 31 of 40 bronchiectatic patients were admitted to the hospital with an acute pneumonic process which did not show clearing by physical or roentgen examination after prolonged treatment.

#### SUMMARY AND CONCLUSIONS

Forty patients with bronchiectasis were admitted to the station hospital at Fort Eustis, Va., during a period of fifteen months. Sixty-seven and five-tenths per cent of the patients in this series had an initial misdiagnosis of primary atypical pneumonia and subsequently were found to have pneumonitis around a preexisting bronchiectasis.

In 75 per cent of the patients the bronchiectasis was unilateral, in two thirds of these it involved the lower lobe of the left lung.

Bronchographic studies should be done in all cases of pneumonia which fail to resolve in a reasonable period (four to six weeks).

11 Brennemann, J. *Dis of Chest* 9:39, 1943

# INFECTIOUS MONONUCLEOSIS

A STUDY OF ONE HUNDRED AND NINETY-SIX CASES

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Infectious mononucleosis, also called glandular fever, presents a problem in diagnosis to physicians, especially those attending large groups of young people. Although it is well known that any young febrile adult suffering with symptoms of a more or less simple sort (cold, sore throat, grip, etc.) should be suspected of having infectious mononucleosis and the necessary laboratory tests made to determine the fact definitely, the procedures are often overlooked. At the Stillman Infirmary, connected with Harvard University, my colleagues and I have observed and attended a large number of young men suffering from this disease. I believe that this is the largest series yet reported and made available for study. From 1935 up to and including June 1943 there were 12,601 men admitted to the Stillman Infirmary for medical care, of whom 249 had a discharge diagnosis of infectious mononucleosis. Of this number, 53 were eliminated as not presenting a typical enough picture of the disease to have their cases included in this study. The cases of the remaining 196 patients are the basis for the material presented here.

This group of 196 patients is 1.5 per cent of the total number of medical admissions—a high incidence when compared with the figures in general hospitals.

At the Peter Bent Brigham Hospital, in Boston, there were 16,907 medical admissions from September 1935 to June 1943. Of this number a diagnosis of infectious mononucleosis was made for only 61 persons, a sharp contrast with the figures from the infirmary.

Spark<sup>1</sup> stated that in the Sydney Hospital, Australia, there had been but 9 inpatients with a diagnosis of infectious mononucleosis, or glandular fever, in the last twenty-two years and in the Royal Prince Albert Hospital but 7 such patients in thirty-two years, at the Royal Alexander Hospital for Children, he was unable to find any inpatient with this diagnosis. Spark expressed the belief that this small number was due largely to the lack of an accurate diagnosis,

as it was not until 1934 that there were any cases of infectious mononucleosis reported in these institutions.

Longcope<sup>2</sup> reported 10 cases which he had gathered from 1909 to 1922 and made the statement that the "disease has been mistaken for tuberculosis, typhoid fever, Hodgkin's disease, and leukemia."

The reasons for the discrepancy between the number of diagnoses of this disease in a college infirmary and in a general hospital are that my series dates only from 1935 and the recognition of infectious mononucleosis is recently more common. Also, a general hospital admits persons of all ages, and infectious mononucleosis is a disease with a special affinity for the young, although Moir<sup>3</sup> reported the case of a patient of 70. In addition, many patients with infectious mononucleosis do not feel ill enough to see a physician, much less be admitted to a general hospital. The students at Harvard University usually do not escape the eye of a physician, as it is a rule that an ill student must report to the department of hygiene and in this way even a mild indisposition is discovered.

The problem of diagnosis in infectious mononucleosis cannot be overemphasized, especially from the point of view of a college infirmary, where many students are far from home and anxious parents are apt to write or telegraph and otherwise seek accurate information. Because the typical blood changes and laboratory criteria for making this diagnosis certain may not appear for many days after the onset of the symptoms, it is naturally unwise without this information to characterize the disease by name, even though one is suspicious of its presence. The variability of the symptoms and physical manifestations with accompanying complications combine to make this illness a diagnostic problem, and, although recent knowledge and interest in the subject have greatly assisted in eliminating some of the difficulties, it is not understood well enough to rule out at all times rather serious diagnostic pro-

From the Department of Hygiene, Harvard University.

<sup>1</sup> Spark, T. E. H. Infectious Mononucleosis. A Problem in Diagnosis, *M. J. Australia* 2: 413, 1942.

<sup>2</sup> Longcope, W. T. Infectious Mononucleosis (Glandular Fever) with a Report of Ten Cases, *Am. J. M. Sc.* 164: 781, 1922.

<sup>3</sup> Moir, J. I. Glandular Fever in the Falkland Islands, *Brit. M. J.* 2: 822, 1930.

cedures. However, too frequently patients have had to endure excision of lymph nodes, sternal puncture or blood transfusion before infectious mononucleosis was suspected and simple laboratory procedures made the diagnosis certain. Extended fatigue and general malaise, which is a common feature of this disease, may excite the patient or his family with the thought of a lingering illness.

Bernstein,<sup>4</sup> discussing 66 cases, has given the most complete and comprehensive report on this subject to date, with a review of the literature which includes 207 references. In this excellent paper, he has described in great detail many of the difficulties which I have only touched on at this point. His thorough observations and description of the symptomatology, clinical manifestations and laboratory data have been a source of great assistance in the preparation of this paper.

Infectious mononucleosis is benign for the most part, but because of the variability of complaints before the onset, the variability of the initial symptoms, the many and varied physical signs and complications of both a mild and seemingly alarming character during the course of the illness, it was felt that the series at the Stillman Infirmary afforded important detailed information of a clinical nature which should be presented for practical purposes in the study of infectious mononucleosis. No attempt has been made to survey the literature on this subject completely nor to present laboratory data or research material past and present. The purpose of the paper is to present observations on a large group of patients whose final clinical diagnosis of infectious mononucleosis has been as accurate as it was possible to make and with as much clinical evidence as I have collected to demonstrate the extreme variability of the disease in all its stages, in the hope that some of the diagnostic problems may be clarified.

#### INCIDENCE

The patients discussed in this study were all students of Harvard University with an average age of 20 years, the youngest being 17 and the oldest 26. The study covers an eight year period of admissions to the Stillman Infirmary, from the fall of 1935 to June 1943. The diagnosis of infectious mononucleosis was made in 249 instances, but in a critical survey of the case histories 53 were excluded because of a negative result of a heterophile test or a blood smear that was not considered typical. Undoubtedly some of these persons whose cases

were excluded were suffering with infectious mononucleosis, and a more complete study would have enabled my colleagues and me to make a certain diagnosis.

Although some authors feel that the disease is more prevalent during certain seasons or months of the year, this has not been borne out by this study (table 1). Inasmuch as the infirmary was not open during the summer months, with the exception of the summer of 1942, the incidence would be much less in this season. Also, the Christmas holidays, of at least ten days to two weeks, would account for the lower number of cases during December.

Epidemics of infectious mononucleosis have been reported by several authors,<sup>5</sup> but I have had no reason to suspect that the disease is highly contagious. The discrepancy in the number of cases from year to year (table 1) is in my opinion due to the fact that the diagnosis was made more frequently when the visiting

TABLE 1—Incidence of Infectious Mononucleosis

Yearly Totals		Monthly Totals 1935-1943	
1935-1936	9	January	21
1936-1937	13	February	27
1937-1938	18	March	22
1938-1939	26	April	23
1939-1940	26	May	29
1940-1941	33	June	10 (partial vacation)
1941-1942	44	July	vacation
1942-1943	22	August	vacation
		September	12 (partial vacation)
		October	34
		November	9
		December	9 (partial vacation)
Total	195	Total	196

personnel of the infirmary suspected the illness and made the necessary tests to prove it. Also, the amount of general illness varies considerably from year to year in the infirmary, the total number of admissions in one year being 1,500 and in another, 2,200. Therefore, I feel that the scale in numbers is not indicative of epidemic proportions in our study. No special precautions were used in the handling of these patients, and they were admitted to an open ward. To my knowledge, there was no instance in which a patient in an open ward has contracted the disease from another patient. Also, no case was reported of one roommate's contracting the disease from another, although the patient may have

4 Bernstein, A. Infectious Mononucleosis, *Medicine* 19 85, 1940.

5 (a) Pfeiffer, E. Drusenfeber, *Jahrb f Kinderh*, 29 257, 1889. (b) Guthrie, C. C., and Pessel, J. F. An Epidemic of "Glandular Fever" in a Preparatory School for Boys, *Am J Dis Child* 29 492 (April) 1925. (c) Moncrieff, A. Two Cases of Glandular Fever in a Family, *Lancet* 1 883, 1932. (d) Nolan, R. A. Report of So-Called Epidemic of Glandular Fever (Infectious Mononucleosis), *U S Nav M Bull* 33 479, 1935. (e) West, J. P. An Epidemic of Glandular Fever, *Arch Pediat* 13 889, 1896.

been ill for several days before being admitted to the infirmary. This experience is different from that which one encounters when dealing with diseases which are obviously highly contagious, such as measles, German measles, chickenpox and mumps.

#### SYMPTOMATOLOGY

One of the most striking features of infectious mononucleosis is the wide variability in the type and severity of its symptomatology. Several of the patients in this series were thought to be neurotic because of their continuous complaints of extended fatigue and malaise although the general physical examination showed nothing abnormal and there was no elevation of temperature. The accurate diagnosis was made only after a blood count and smear proved to be typical of this disease. On the other hand, in contrast to this mild onset, many of the patients were prostrated, with high fever, resembling the picture of typhoid or severe streptococcal infection of the throat. Between these two extremes is the great majority, with such a wide variability of symptoms and physical signs that unless adequate thought had been given to infectious mononucleosis the diagnosis would have gone into the general category of infections of the upper respiratory tract.

Sore throat was undoubtedly the most common symptom of which these patients complained. Although it did not occur as the presenting symptom in more than 50 per cent of the cases, it developed at some time during the course of the illness, so that all except 35, or 18 per cent, of the patients had this complaint at some time during the infection. The degree of sore throat was variable, being of a mild nature in some, described as merely "dry," while in others it was so severe as to cause pain when the patient was swallowing liquid.

Headache often heralded the onset of the disease, being so mild in some cases that little attention was given to it while in others it was extremely severe, of enough concern to the physician to make him question whether he might be dealing with typhoid or spinal meningitis.

Fatigue and general malaise were both frequent companions to other symptoms, often preceding the more acute onset of the illness by some days or even a week or two.

Gastrointestinal symptoms were not particularly prevalent, and, with the exception of patients in whom jaundice, nausea and vomiting later developed, it occurred very infrequently. Pfeiffer<sup>51</sup> and Bernstein<sup>4</sup> both mentioned that the frequency of constipation is striking, but it was present in only a few of these patients. It

seemed worthy of little consideration as a symptom of the disease, since any active patient confined to bed may become constipated. Diarrhea also was an infrequent symptom, the only case in which it was serious is discussed in the paragraph on complications. Abdominal pain was present in only a few instances in this series and was usually accompanied by diarrhea. A report of 1 case in which abdominal pain was indicative of a condition in the abdomen requiring surgical treatment is also discussed in the paragraph on complications. In this case, an acutely diseased appendix was removed. This example contrasts sharply to abdominal pain and the sequelae as described by Davidsohn,<sup>6</sup> who, in his experience, never found a typical acutely inflamed appendix when operation was performed but found what he felt to be a condition due to a direct complication of infectious mononucleosis.

Anorexia was a common symptom, its degree and duration depending largely on the severity of other symptoms accompanying the illness.

A presenting symptom of stiff or sore neck was usually referable to the swollen cervical lymph nodes. The onset of the lymphadenopathy was usually found in this area and, for some unknown reason, often on the left side.

The symptoms of ordinary infections of the upper respiratory tract, with nasal congestion, fever and chills, were conspicuous. However, true chills occurred infrequently, and when they did occur they were accompanied by high temperatures. Generalized aches and pains such as one would associate with "grip" were often present. Pain on moving the eyeballs was mentioned by several in describing their initial symptoms. Cough, a mild presenting symptom, was noticed subjectively by 11 patients. Sweating and dizziness were seen only occasionally.

In table 2 are listed all the presenting symptoms as a single complaint and also combined with two or more symptoms. It will be noted that a great number of patients had more than one symptom but also that a considerable number complained of only one symptom at the time of admission, sore throat being the most frequent.

#### PHYSICAL SIGNS

*Inflammation of the Throat*—Sore throat is the outstanding subjective symptom of infectious mononucleosis. It was the initial symptom of 96, or about 50 per cent, of the patients in this series, many of whom complained of a sore or "dry" throat for days or even weeks preceding the appearance of other symptoms. One hundred

<sup>6</sup> Davidsohn, I. Infectious Mononucleosis, *Am J Dis Child* 49 1222 (May) 1935.

and sixty-one, or 82 per cent, complain of a sore throat at some time during the course of the illness

The objective observations concerning the throat were extremely varied. In 31 patients, the throat was normal in appearance throughout the course of the illness, in 56, it was mildly injected. In 66 the throat was moderately red for several days, and in 43 it showed either pronounced follicular tonsillitis or an ulcerative pharyngitis with sloughing of tissue. When the throat was found to be noticeably injected, it usually remained sore for a week or ten days and was the most annoying symptom, as even the swallowing of water caused pain and discomfort.

Smears from the ulcerated lesions revealed a mixture of streptococci, fusiform bacilli and spirochetes.

in all cases of Vincent's angina to be sure that blood smears and heterophile tests are made to assure an accurate diagnosis.

*Fever*—Fever was present in all except 22, or 11 per cent, of the patients in this series. The elevation of the temperature and its duration were variable. The highest fever encountered was 105 F (in 1 patient only and continuing at that level for three days) and the longest duration of fever was thirty-two days (in just 2 patients). Seventy-seven, or 39 per cent, of the patients had an elevated temperature for less than five days. Thirty-eight patients (19 per cent) had fever from ten to fifteen days, and 27 (13 per cent) had fever of more than fifteen days' duration.

The fever is of the spiking nature and has no definite course. In some cases the high point of the fever was in the morning, in others, at

TABLE 2—Presenting Symptoms of Patients with Infectious Mononucleosis

Single Chief Complaint	Combination of Two Presenting Symptoms													Combination of Two or More Symptoms	Grand Total
	No	Sore Throat	Fatigue	Headache	Cold	Fever	Enlarged Nodes	General Aches and Pains	Gastrointestinal Symptoms	Chills	Soreness of Eyes	Cough	Sweating	Dizziness	Ear Aches
Sore throat	33			4	12	1	8	10				1			27
Fatigue	14														69
Headache	6	4			2	1	1	3			2				25
Cold	7			2		1		1							32
Fever	1	1			1	1		5	1	4					28
Glands	4														35
General aches and pains	1	10		3	1	5				2	1				0
Gastrointestinal symptoms	2					1								1	13
Chill	0					4		2							5
Soreness of eyes	2			2				1							6
Cough	0	1													10
Sweating	0														6
Dizziness	1								1						2
Earache	0														4
Totals	71	16	0	11	16	14	9	22	2	6	3	1	0	1	0
															262
															434

*Vincent's Angina*—Tender, bleeding gums, often spongy and swollen and sometimes ulcerated, appeared in 13 patients in this series. In all except 2 of these, this condition was accompanied by a sore throat, usually complicated by ulceration of the tonsillar pillars or the pharyngeal wall. The involvement of the gums frequently preceded the inflammation of the throat and in some cases was more severe. This often led to a diagnosis of Vincent's angina early in the disease, which was later corrected by the heterophile test and blood smear. From this experience, I feel that many patients who display nothing more than bleeding or tender gums, which may be either swollen or spongy or both, may well have infectious mononucleosis. Since this condition may closely simulate a purely local infection or others of a more serious nature, such as pharyngeal diphtheria, it would be wise

noon, and in still others it was in the late afternoon or evening. In a number of cases the temperature would return to normal for a period of twenty-four hours and then would again become elevated for four or five days. The amount of fever and its duration did not seem necessarily related to either the sore throat or the blood count. In many cases in which the sore throat was a minor complaint, the temperature was quite high and remained elevated for many days. There was no direct relationship between the amount of fever and the lymphadenopathy or between the fever and splenomegaly. Several instances were noted in which by the time the lymph nodes became enlarged, the spleen palpable and the blood smear diagnostic the temperature had abated and the patient was feeling much better. In some of the cases in which a diagnosis of neurosis was made during



the early part of the disease because of continued fatigue and a noncontributory physical examination, including a normal temperature, a slight fever may have been present at some time during the twenty-four hours. These men, because of normal results of physical examination and absence of fever at the time they reported to the clinic, were not hospitalized and were forced to carry on their usual routine. It is little wonder that they continued to return to the clinic with the complaint of extreme fatigue and exhaustion.

*Lymphadenopathy*—The common conception in the past that enlargement of lymph nodes always accompanies infectious mononucleosis did not prove true in this series. Thirty-two, or 17 per cent, of the patients had no enlargement of peripheral nodes at any time during the course of the illness, although the clinical course, the hemogram and the heterophile examination led to a diagnosis of infectious mononucleosis. Tidy and Daniel<sup>7</sup> stated that infectious mononucleosis with no glandular enlargement is rare and suggested that the patients having no such enlargement must have enlarged mesenteric or mediastinal glands. This, of course, cannot be proved or disproved in a study of this type.

The striking feature of the lymphadenopathy in this series is that in the great majority of cases it did not appear early in the disease. Definitely enlarged superficial lymph nodes were noted in only 19 patients at the time they appeared with their original complaints. Many of the remaining patients acquired enlarged superficial lymph nodes in several days or a week after the onset of illness, but a moderate number had no lymphadenopathy until the other symptoms had abated and they were well on their way to recovery. In several cases no glandular enlargement was noted until two or three weeks after the onset. Landes<sup>8</sup> reported the case of a seriously ill young man who, despite a positive heterophile reaction and a careful daily examination, did not have enlarged nodes until twelve days after he entered the hospital, which was twenty-two days after the onset of the symptoms.

Generalized glandular enlargement was noted in only 10 cases.

It is difficult to state the exact size of the lymph nodes in this illness. Nodes which I considered slightly palpable, might be described as being of the size of a small pea, for glands

which I considered moderately palpable, a large pea would be descriptive, and glands which were found to be easily palpable were about the size of a hazelnut. In no instance were the glands found to be extremely large and matted together. I suggest that if such a condition occurs, a diagnosis other than infectious mononucleosis be considered.

Enlargement of the cervical lymph nodes was the most common chain involvement and was present in 149 patients. In 82 of this number they were mildly enlarged, in 57, moderately enlarged, and in 10, easily palpable.

Sixty patients were found to have enlargement of the axillary nodes, in 45 of these they were mildly enlarged, in 14, moderately enlarged, and in 1, easily palpable.

Enlargement of the occipital nodes was noted in only 5 patients.

It is to be observed that in this entire series of 196 patients there was never lymphadenopathy in any other region when cervical nodes were not palpable.

It should be borne in mind that one must differentiate enlargement of the cervical lymph nodes from enlargement of the cervical salivary glands. One of the frequent errors made in diagnosis is the not too careful consideration of this point. Students have frequently been sent to the infirmary with a tentative diagnosis of infectious mononucleosis, when closer examination revealed that they were actually suffering from mumps. Moreover, in all schools and colleges, one frequently encounters epidemics of German measles. It is my opinion that in the great majority of instances German measles is accompanied with the greatest enlargement of the lymph nodes of the occipital and postauricular chains, while in infectious mononucleosis, enlargement of the occipital and postauricular lymph nodes occurs only after one can easily palpate larger anterior cervical or inguinal nodes.

The lymphadenopathy is usually transient and in the majority of cases has completely abated within two or three weeks. In some cases, however, the lymph nodes may remain slightly enlarged for a period of a month or two, but in no case was any notable lymphadenopathy encountered after two months.

*Splenomegaly*—The spleen was palpable in 91 patients. Although this is less than half of the number of patients observed, it makes one realize that the palpability depends largely on the examiner, and when one discusses whether or not the spleen is palpable it should be remembered that the differences of opinion of the examiners must be considered.<sup>4</sup> Most of the patients in this study were examined by the same physicians,

<sup>7</sup> Tidy, H. L., and Daniel, E. C. Glandular Fever and Infectious Mononucleosis, with an Account of an Epidemic, *Lancet* 2 9, 1923.

<sup>8</sup> Landes, R., Reich, J. P., and Perlow, S. Central Nervous System Manifestations of Infectious Mononucleosis. Report of a Case, *J. A. M. A.* 116:2482 (May 31) 1941.

and an effort was made to feel the spleen daily during the time that the patient was confined to the infirmary and as many patients as possible were seen at regular intervals after they were discharged

Of the 91 patients with a palpable spleen, 67 had spleens which were barely felt and 15 had spleens which were easily palpable, in 9 instances the spleen was enlarged about 2 fingerbreadths below the left costal margin. In several cases the spleen was definitely tender, but for the most part no pain was evidenced on palpation

In general, the recession of the size of the spleen followed the diminution in the size of the lymph nodes, but in some instances the spleen was still palpable as late as a year after the acute infection had subsided

There was no patient in this series in whom splenomegaly was present without lymphadenopathy

*Jaundice*—Jaundice, although not a frequent complication of infectious mononucleosis, occurred in 10 of the patients in this series. It was noted that in most cases the jaundice did not occur for five or six days after the onset of the illness and in some instances was as late as ten days to two weeks in becoming evident

The jaundice was definite in character, with icterus of the skin, scleras and mucous membranes. The urine was dark and gave a positive reaction for bile. For the majority of patients in whom jaundice was present, a diagnosis of infectious mononucleosis had already been made, and in some instances the acute febrile reaction of the disease had passed

I have no idea what the mechanism is that produces the complication of jaundice with infectious mononucleosis. I do not feel that it is due to obstruction of the common bile duct by glandular enlargement, as there was never any change in the color of the stools or any itching of the skin. The usual duration of jaundice as a complication was not more than two weeks, and it was not in any way related to the height or duration of the fever, to the lymphadenopathy or to the splenomegaly. On examination of these patients the liver was not enlarged or tender. The majority of the students who had jaundice experienced anorexia, nausea and vomiting which lasted for a day or two

In comparing the jaundice which complicates infectious mononucleosis with catarrhal jaundice, I was unable to note any difference in the symptoms, physical signs or clinical course

*Neurologic Signs*—Although neurologic manifestations have been described as a complication of infectious mononucleosis by Epstein and

Dameshek,<sup>9</sup> Johansen<sup>10</sup> and Landes and associates,<sup>8</sup> no objective signs of this type were evident in any patient in this series. Headache, however, was a common symptom. In some instances it was of such severity and duration that had not a definite diagnosis of infectious mononucleosis been established a lumbar puncture undoubtedly would have been done in order to rule out involvement of the central nervous system by some other process

*Rash*—Rash occurred in only 10 patients. This is in rather sharp contrast to its occurrence in a series of 91 cases reported by Templeton and Sutherland<sup>11</sup> in which rash appeared in 18.5 per cent of the cases. Since a rash may occur from many different causes, it is unwise to blame a disease for the appearance of a rash which is simultaneous. Many persons manifest a rash as a result of any of a number of drugs ingested during an illness. Likewise, some persons exhibit a transient rash which is caused by fever alone

In my experience the making of a differential diagnosis in the early stages between infectious mononucleosis and German measles is difficult. If rash is present and if there is enlargement of lymph nodes, especially of the posterior cervical nodes, which often occurs in persons suffering from German measles, the two illnesses may easily be confused. Even when laboratory studies are made it is often impossible to be certain, since the hematologic changes may not become evident for several days. German measles, like infectious mononucleosis, is common among persons of college age, and many students in this series who were given an initial diagnosis of German measles were later found to have infectious mononucleosis

The rash which appeared in the 10 subjects in this study closely resembled that of mild German measles, was morbilliform and transient and did not last over forty-eight hours

Although I feel that it is wise to keep the rash in mind in connection with infectious mononucleosis, I do not feel that it is characteristic enough in itself to be relied on as a diagnostic feature

#### BLOOD

The diagnosis of infectious mononucleosis cannot be made unless either the heterophile reac-

9 Epstein, S. H., and Dameshek, W. Involvement of the Central Nervous System in a Case of Glandular Fever, *New England J. Med.* **205** 1238, 1931

10 Johansen, A. H. Serous Meningitis and Infectious Mononucleosis, *Acta med. Scandinav.* **76** 269, 1931

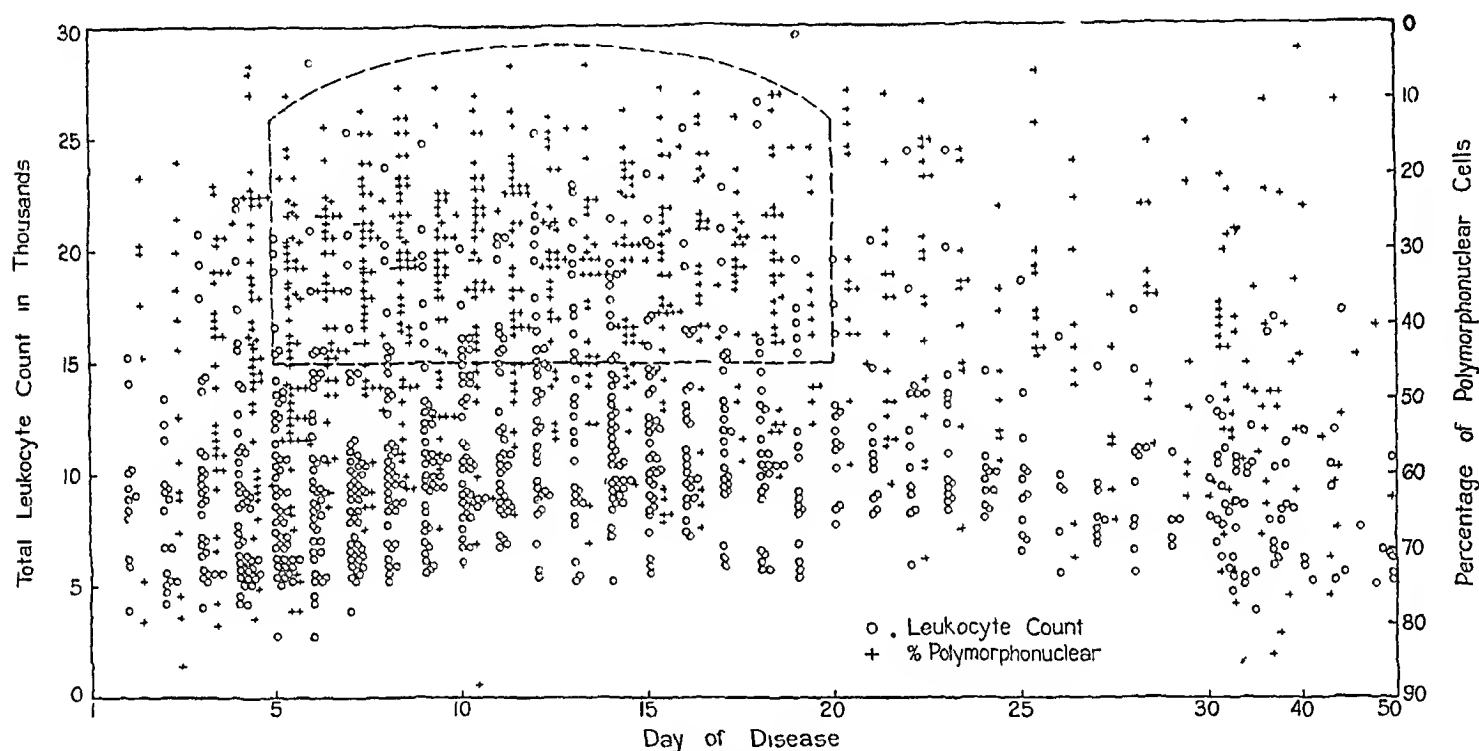
11 Templeton, H. F., and Sutherland, R. T. The Exanthem of Acute Mononucleosis, *J. A. M. A.* **113** 1215 (Sept. 23) 1939

tion is positive in high dilution or the blood smear is typical

In this series, the diagnosis was not made without what I consider a typical blood smear for this disease, which means that the percentage of neutrophilic cells was below 40 and in the smear there were a large number of so-called atypical lymphocytes. The atypical lymphocyte, as it appeared in these smears, was a large mononuclear cell with a pale-staining, rather fragile-looking cytoplasm that curled over on itself and had a large nucleus. It is believed by most observers that this cell is a lymphocyte. Dameshek<sup>12</sup> remarked that in a smear of a patient with infectious mononucleosis the size and appearance of a lymphocyte is variable.

In my experience the appearance of the smear has been easy to differentiate from that of an acute or chronic leukemia. The normal platelet count, the normal appearance of the red cells, the total absence or only occasional appearance of a cell that may be mistaken for a blast and the appearance of large numbers of atypical lymphocytes, together with a normal red cell count and normal hemoglobin content, make the diagnosis of infectious mononucleosis evident.

In 83, or 42 per cent, of the patients in this series, the initial white blood cell count was elevated above 10,000, and in 33, or 17 per cent, of these it was above 15,000. It is evident from these figures that the leukocyte count in itself is of little assistance in making an accurate diagnosis.



Blood counts of all patients with infectious mononucleosis admitted to Stillman Infirmary during the period 1935 to 1943

If one observes the development of changes in the blood picture, it will be noted that early in the disease there is no reduction in the polymorphonuclear cell count and the so-called atypical lymphocyte appears. There may be few of these in the beginning, but they gradually become more numerous and at the same time the number of polymorphonuclear cells decreases. The reduction in polymorphonuclears may be alarming. In 1 of the patients in this study they made up only 3 per cent of the total number of white blood cells. In several cases the count was below 10 per cent, and a drop to 20 per cent was not at all unusual.

For the most part, the initial white cell count is normal or only slightly elevated. In a fair percentage of cases it may never exceed a total of 10,000. In some instances, however, it may rise far above this figure, as shown by 1 of these patients with a count of 31,000.<sup>13</sup> Counts above 25,000 were obtained in 7 instances. There does not seem to be any direct relationship between the total leukocyte count and the reduction of polymorphonuclear cells. In general, however, it was noted that some of the patients with higher counts had a low percentage of polymorphonuclears in the smear. Bernstein,<sup>4</sup> in reviewing the literature, reported 10 cases with

<sup>12</sup> Dameshek, W. Hematology, New England J Med 224 729, 1941

<sup>13</sup> Since this study was completed, I have observed a patient with infectious mononucleosis with a white blood cell count of 41,000.

counts over 40,000, these occurring in children under 10 years of age

If one observes the chart of all the blood counts taken in this series, it will be noted that on an average the leukocyte count is highest from the fifth to the twentieth day of the illness and that the reduction in the percentage of the polymorphonuclear cells also occurs during this period. The chart also shows that the abnormality in the total leukocyte count and the reduction of the polymorphonuclear cells are of short duration and return in most cases to a comparatively normal figure within two weeks. This continues gradually, so that within a period of two months the counts are back to normal. Occasionally one finds that after two months some of the atypical lymphocytes are still present in the smear, but the percentage of these is so small that it would be dangerous to make a diagnosis of infectious mononucleosis on the appearance of these cells alone.

Although the chart represents an average of all the blood counts taken, several of the students were ill for as long as fourteen days before a definite diagnosis of infectious mononucleosis was made on the basis of the blood smear. In most cases blood smears were repeated daily, as one of the eccentricities of this disease is that the smear is not suggestive early in the illness and if subsequent blood smears are not made the diagnosis may be overlooked. In a large percentage of the cases the blood smears were not typical for many days after the onset of the illness, and when they did become diagnostic the acute febrile reaction was over and the patients were recovering. This has been the experience of others.<sup>14</sup> In 122 cases the original blood smear was suggestive or typical enough of the disease to make an immediate, accurate diagnosis, but it must be remembered that a large number of these students did not report to the infirmary for many days after the onset of symptoms.

A few of the patients, especially those who were discharged from bed before complete recovery and whose symptoms continued for some weeks so that they were forced to return to the infirmary, were found to have a blood smear still characteristic of infectious mononucleosis. In 1 of these instance the polymorphonuclear count was reduced to a lower level than it had been at the time of the patient's original admission.

Biopsy of a cervical lymph node was performed in only 1 case. This was done, however, not because the diagnosis of infectious

mononucleosis was in question but because clinical evidence showed that a tuberculous lymphadenitis might be complicating the illness. Sternal puncture was never performed as a diagnostic procedure.

#### HETEROPHILE TEST

Paul and Bunnell<sup>15</sup> in 1932 made what is considered the greatest contribution toward making an accurate diagnosis of infectious mononucleosis. Called the heterophile test, it consists of agglutinations of sheep cells with the serum of patients with the disease. At that time they demonstrated high agglutinations of sheep cells with the serums of such patients and reported 4 cases. In 1 the patient's serum agglutinated sheep cells at the high dilution of 1:1,024, in another, on the thirteenth day of the illness, agglutinins were present in a dilution of 1:128, and in another at the height of the illness agglutinins were present at 1:152, in the fourth case, tests during early convalescence showed agglutinins in dilutions as high as 1:256. Among many cases of various pathologic conditions studied by Paul and Bunnell at that time, a titer of above 1:32 was not observed except in the serums of persons with serum disease and with infectious mononucleosis.

In 1929 Davidsohn<sup>16</sup> discovered that the serums of 42 per cent of normal persons agglutinated sheep cells in a dilution of 1:4 while those of 95.8 per cent produced no agglutination in any dilution. He also found evidence to show that patients who had recently been suffering from serum sickness showed an agglutination of 1:32 or higher.

Heterophile tests were done on 143 patients, or 73 per cent, in this series. Of these, the agglutination of sheep cells occurred in a dilution of 1:64 or higher in 118 cases, and the serums did not agglutinate the cells in this dilution in 25. These 25 serums might have shown agglutination if enough tests had been done. In my experience, it was a common occurrence that a heterophile test made early during the infection might not show agglutination in a high titer while the serum from the same patient taken several days or a week later would show the presence of agglutinins in a dilution of 1:64 or higher.

With this experience, it is extremely difficult to evaluate properly the percentage of persons who are undoubtedly suffering from infectious

14 McKinlay, C. A. Infectious Mononucleosis, *J. A. M. A.* **105**:761 (Sept. 7) 1935.

15 Paul, J. R., and Bunnell, W. W. The Presence of Heterophile Antibodies in Infectious Mononucleosis, *Am. J. M. Sc.* **183**:90, 1932.

16 Davidsohn, I. Further Studies on Heterophilic Antibodies in Serum Sickness. *I. Immunol.* **18**:31 1930.

mononucleosis but who never have a positive heterophile reaction during the course of their illness. I feel, however, that such cases do occur.

In my opinion the 25 patients in this series who had a negative reaction had classic clinical infectious mononucleosis, as manifested by the symptoms, physical signs and typical blood smears. For none of them was the polymorphonuclear count higher than 40 per cent. For several the polymorphonuclear cells made up less than 15 per cent of the total count, with the greatest percentage being between 20 and 35. Moreover, the smears showed a high percentage of atypical lymphocytes.

Because of some technical reason the heterophile test was not done on 53 persons in this group, but caution was used to determine accurately the diagnosis of infectious mononucleosis. In this group the symptoms, physical signs and blood smears were as typical of the disease as were those of patients who had a positive heterophile reaction. As a matter of fact, the average of polymorphonuclear cells was lower in this group than in those that had a positive heterophile reaction. The reason for this is that patients who did not have a significantly lowered polymorphonuclear count were excluded. Had a heterophile test been done, the results would undoubtedly have been positive in a high percentage of cases.

Although an attempt was made to perform follow-up heterophile tests in this study, it was not feasible. However, in the few that were done, it was found that the results were negative within three months after the patient's discharge from the infirmary.

#### COMPLICATIONS

One is impressed when reading the literature by the frequent mention of complications with infectious mononucleosis. It is my feeling, however, that this disease is attended with the risk of no more complications than an ordinary infection of the respiratory tract and any complication is usually that of a concomitant infection or the exacerbation of an old process. No complication was noted in any patient in this series that could be directly attributed to infectious mononucleosis as the etiologic agent.

In 1 instance a patient acquired the syndrome of nephrosis, with large amounts of albumin in the urine, a drop in the total protein content and reversal of the albumin-globulin ratio in the blood. He also accumulated large amounts of edema fluid, including ascites. However, this patient had had the same syndrome two years before after what appeared to be an ordinary

infection of the upper respiratory tract. After several weeks of rest in bed a spontaneous diuresis occurred, the edema fluid disappeared, the albuminuria cleared and the blood chemistry reverted to normal. This man is now well, with all laboratory findings normal.

Although a small amount of albumin was noted in the urine of several patients at the height of the febrile illness, this cleared quickly, and in no instance was the urine pathologic or even suggestive of an acute nephritic process.

Another patient who previously had bouts of severe diarrhea, with a positive test for occult blood in the stool, had an exacerbation of this process during an acute phase of infectious mononucleosis. Although the symptoms and the appearance of the rectal and sigmoid mucous membrane suggested early ulcerative colitis, these symptoms also cleared within a short time, only to recur some time later without any definite discoverable reason. I do not feel that the infectious mononucleosis was more responsible than any acute infection would be in the exacerbation of the intestinal symptoms, moreover, it is my feeling that nervous tension and fatigue were largely responsible. Two years later this patient still has paroxysmal bouts of diarrhea, but as far as I know the typical syndrome of ulcerative colitis has never developed.

In 1 case an acute otitis media developed about twenty days after the onset of symptoms and five days after the patient's admission to the infirmary. The abscess was incised, and streptococci were cultured from the secretion. The patient continued to have infection in the mastoid cells, and twelve days after the abscess was incised mastoidectomy was performed. This is the only instance in this series in which a bacterial infection of an ear occurred which required paracentesis and later mastoidectomy. It seems unlikely that one would attribute infectious mononucleosis as the direct cause of this complication.

Although nausea and vomiting were present in some of these patients, especially those who later acquired jaundice, it was not a prominent symptom.

Abdominal pain occurred but rarely and, with 1 exception, caused no concern as to whether an acute condition requiring surgical intervention was present. The exception was a student who twelve days after the onset of his illness and while on the way to recovery showed typical signs and symptoms of acute appendicitis. Appendectomy was performed, and an acutely inflamed appendix was removed. This was more likely a coincidental occurrence than cause and effect.



I do not feel that cardiac changes observed in patients with infectious mononucleosis can be attributed to this illness. Certainly a systolic murmur is not always indicative of pathologic conditions in the heart. It seems reasonable to assume that a systolic murmur<sup>17</sup> may be a coincidental finding, and, moreover, it is common knowledge that although no murmur is present when the heart rate is slow a definite systolic murmur may appear when it becomes rapid. It makes no difference whether the elevation of the heart rate is due to fever or to exercise. Bradshaw<sup>18</sup> reported a case of mitral stenosis following infectious mononucleosis. However, none of the patients in my group displayed any cardiac abnormality.

Gooding<sup>19</sup> reported 1 case of death of a patient with infectious mononucleosis as a result of bronchial pneumonia, and Du Bois<sup>20</sup> called attention to empyema as a complication. However, although a few of the subjects had severe cough as a predominating symptom, there was no instance of definite pneumonia.

#### HOSPITALIZATION

It must be remembered that the recorded days of hospitalization do not necessarily signify the duration of this illness. Many of these busy—or careless—students did not report for medical care for several days or even weeks following the onset of symptoms and reported only when their illness had reached a stage where they were unable to continue their normal activities. Even so, because of the large group in this series, it is possible to report a great diversity in the length of the hospital stay of these patients, owing of course to the extreme variability in the symptoms and clinical manifestations of the illness. Twenty-nine, or 15 per cent, of this group were hospitalized for less than five days. The greatest number, 88, or 45 per cent, were in the hospital for between six and ten days. Forty-two, or 21 per cent, were confined for a period of from ten to fifteen days, 23, or 11 per cent, from fifteen to twenty days, and 12, or 6 per cent, from twenty to twenty-five days. Two patients were obliged to remain for thirty-one days.

Discharge from the infirmary did not always indicate that the patients were ready for full

activity. Many complained of extreme fatigue and easy exhaustion for several weeks after their discharge, and some were required to have a period of convalescence at home.

#### RECURRENCES AND RELAPSES

In any illness it is most difficult to separate a recurrence from a relapse or from a continuation of the same condition. However, in dealing with a disease as benign for the most part as infectious mononucleosis, there were many instances of a discharged patient's returning with symptoms of the same illness. Since the patients were students, the necessity for taking current examinations, intervening vacations and many other personal reasons were excuses for an early discharge, against advice.

In my experience, although a patient has a significant increase in the total white blood cell count with a definitely lowered polymorphonuclear count he may feel well and be eager to return to his normal activities. Should he be allowed to do so, it is more than possible that he would become fatigued, with a return of subjective symptoms and fever. If such is the case, it must be considered that this is a continuation of the illness, not a recurrence or a relapse. There was no instance in this series of a continuation, recurrence or relapse when I was absolutely certain that the patient had fully recovered as manifested subjectively and objectively, with at least the beginning of a return to normal of the white blood cell count and the smear. On the other hand, patients who were discharged when it was felt that more rest in bed was needed and the hemogram was still abnormal returned in a few days, or even weeks, showing again the typical syndrome of infectious mononucleosis. There were 8 such instances in this series. Four persons were readmitted to the infirmary within a period of three weeks after discharge, 2 were readmitted after a period of five weeks, 1 was readmitted after two months, and another, three months after the infection. In all of these instances the patients stated that at no time since the original discharge from the infirmary had they felt completely well and during the entire interval had had a continuation to some degree of the symptoms for which they were originally confined.

#### THERAPY

There is no specific therapy for infectious mononucleosis. Many of the more severe manifestations of the illness could be avoided if the patient were put to bed at once, and from experience it is my opinion that, although the symptoms

17 Contratto, A. W. Significance of Systolic Cardiac Murmurs in College Students, *New England J Med* **228** 499, 1943.

18 Bradshaw, R. W. Mitral Stenosis Following Infectious Mononucleosis, *Ohio State M J* **27** 717, 1931.

19 Gooding, S. E. F. On Glandular Fever or Infectious Mononucleosis, *Practitioner* **127** 468, 1931.

20 Du Bois, A. H. Pathogenesis of Morocytic Angina, *Acta med Scandinav* **73** 237, 1930.



may be mild, rest in bed and the usual symptomatic treatment are the wise approach

In cases of severe headache or extreme discomfort of the throat, codeine in doses of  $\frac{1}{2}$  or 1 grain (0.03 or 0.06 Gm) by mouth every four hours was needed. Irrigations with saline solution were administered for sore throat. For ulcerations of the throat or Vincent's angina hydrogen peroxide diluted 1 to 3 was found helpful if used as a wash every two hours. Although neoarsphenamine has been used in therapy for this illness by oral application and intravenously, I do not believe it is necessary or helpful. Likewise, in the few cases in this series in which sulfadiazine was administered, no benefit was noted. Nicotinamide seemed to relieve some patients who had severe Vincent's angina. Excess salt was given to patients who had profuse sweating. In persons in whom jaundice occurred accompanied by nausea and vomiting it was necessary to replenish body fluid, salt and dextrose by intravenous injection. Also, in some instances in which the condition of the patient's throat was such that swallowing was painful, intravenous injections of dextrose and isotonic solution of sodium chloride were used with great benefit.

It is desirable to emphasize the convalescent period to patients discharged from a hospital after this illness. The simple therapy of enough rest, sleep, proper diet and fresh air will cer-

tainly hasten the return to normal from a disease in which extended fatigue is the most insidious effect. This is especially true of young people, who have the greatest affinity for infectious mononucleosis, since they are at the present time leading particularly strenuous lives.

#### CONCLUSIONS

Infectious mononucleosis is a benign illness.

The complications encountered in this series were varied, but they are believed not to be directly referable to the disease.

Infectious mononucleosis may be accompanied notably by lymphadenopathy, splenomegaly, jaundice, Vincent's angina, ulcerations of the throat, fever, a conspicuous change in the blood picture and a number of complaints identical with those common to an ordinary infection of the upper respiratory tract.

Accurate diagnosis is difficult because of the variability of the symptoms and clinical manifestations. The problem and major difficulty in this disease is the making of a differential diagnosis, which can easily be accomplished by the heterophile test, blood count and smear. I have pointed out the importance of making not only more than one but frequent tests and smears during the course of the illness, since a peculiarity of infectious mononucleosis is that there is more often than not a delay of days or even weeks before the hematologic changes are conclusive enough to permit an accurate diagnosis.

# SPONTANEOUS PNEUMOTHORAX COMPLICATING BRONCHIAL ASTHMA

## REPORT OF TWO CASES AND CONSIDERATION OF POSSIBLE MECHANISMS INVOLVED IN ITS PRODUCTION

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Spontaneous pneumothorax is a potentially fatal complication of bronchial asthma, the diagnosis of which may not be obvious. In a recent review of the world literature on this subject Maccone<sup>1</sup> collected 27 cases. Piaggio Blanco and García Capurro<sup>2</sup> suggested that the ease with which this condition may be missed accounts for its apparent rarity. Although most authors have failed to mention bronchial asthma as a precursor of spontaneous pneumothorax the casual manner in which others<sup>3</sup> have mentioned it does not indicate extreme rarity. Questioning of physicians has revealed several who have observed one or more unreported cases.

Spontaneous pneumothorax occurs as a complication of bronchial asthma chiefly in young persons, of both sexes. The average age of the patients whose cases were collected by Castex and Mazzei<sup>4</sup> was 32 years, and they did not include the children of 1¼ and 2<sup>5</sup> and 4<sup>6</sup> years of age whose cases were reported elsewhere. The oldest reported patient was 59 years of age.<sup>7</sup> The mode of onset is as variable as that of spontaneous pneumothorax occurring in otherwise

normal persons.<sup>8</sup> Bottero<sup>9</sup> suggested that the symptoms may depend on the rapidity of the development of the pneumothorax. Dyspnea is usually present and definitely subjectively different from that ordinarily accompanying asthmatic attacks.<sup>10</sup> Pain is an almost constant feature, but it may be absent, particularly in cases of recurrent pneumothorax. It is usually pleural and may radiate to the flank, a sense of constriction in the chest is frequently noted. Casiello<sup>10</sup> reported a case in which the clinical picture suggested a coronary occlusion. Though there may be no symptoms to suggest the development of a pneumothorax during an asthmatic attack,<sup>11</sup> the time of onset of the pneumothorax can usually be established by the onset of pain or of a changing type of dyspnea. Left-sided pneumothorax is slightly more common than right. The condition often recurs on the same<sup>12</sup> or on the opposite<sup>13</sup> side. Four cases of bilateral

8 Leggett, E. A., Myers, J. A., and Levine, I. Spontaneous Pneumothorax, Report of Thirty-One Cases, *Am Rev Tuberc* **29** 348 (March) 1934

9 Bottero, A. Il pneumotorace spontaneo negli asmatici, *Athena* **8** 372 (Aug.) 1939

10 Casiello, A. Neumotorax espontaneo benigno y asma, *Arch argent de enferm d ap respir y tuberc* **5** 164 (March-April) 1937, *Neumotorax espontaneo benigno y asma*, *Rev med del Rosario* **26** 961 (Oct) 1936

11 (a) Emerson, C. P., and Beeler, R. C. An Unusual Case of Double Spontaneous Pneumothorax, *Am J Roentgenol* **10** 126 (Feb.) 1923. (b) Spivacke, C. A. Asthma with Pneumothorax, *M J & Rec* **122** 10 (July 1) 1925

12 (a) Maccone<sup>1</sup>. (b) Harvey, C. Asthma Complicated by Spontaneous Pneumothorax, *M J Australia* **2** 950 (Dec 3) 1938. (c) Arguelles Casals, C., Alvarez Garcia, V., and Pedraza, R. O. Neumotorax espontaneo en el asma, *Rev de cien med* **1** 90 (Sept.) 1938. (d) Fornet, B. Rezidivierender Spontanpneumothorax bei Bronchialasma, abstracted, *Zentralbl f d ges Tuberk-Forsch* **33** 62 (June) 1930. (e) Fuchs, A. M. Spontaneous Pneumothorax in an Asthmatic Treated with Iodized Oil, *New York State J Med* **39** 791 (April 15) 1939. (f) Symes-Thompson, H. E. Spontaneous Pneumothorax, *Lancet* **2** 791 (Oct 11) 1930

13 Ribeiro de Carvalho, J., and da Silva Lacaz, C. Pneumothorax espontaneo bilateral por emphysema astmatico, *Ann paulist de med e cir* **37** 241 (March) 1939

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1 Maccone, V. Il pneumotorace spontaneo nell'asma, *Ann Ist Carlo Forlanini* **4** 257 (March-April) 1940

2 Piaggio Blanco, R. A., and Garcia Capurro, F. Neumotorax espontaneo y enfisema subcutaneo y del cuello en el curso del asma, *Arch urug de med, cir y especialid* **16** 367 (April) 1940

3 (a) Myers, J. A. *Diseases of the Chest*, edited by M. Fishbein, New York, National Medical Book Company, Inc., 1935. (b) Rowe, A. H. *Bronchial Asthma*, in *Nelson's Loose Leaf Medicine*, New York, Thos Nelson & Sons, 1937, vol 3, p 457. (c) Hamman, L. A Note on the Mechanism of Spontaneous Pneumothorax, *Ann Int Med* **13** 923 (Dec.) 1939

4 Castex, M. R., and Mazzei, E. S. Pneumothorax spontane dans l'asthme, *Presse med* **46** 529 (April 6) 1938

5 Rasenack, W. Ueber 20 Falle von Spontanpneumothorax im Kindesalter, *Ztschr f Kinderh* **58** 95, 1936

6 Gunther, cited by Bottero<sup>9</sup>

7 Faulkner, W. B., Jr., and Wagner, R. J. Fatal Spontaneous Pneumothorax and Subcutaneous Emphysema in an Asthmatic, *J Allergy* **8** 267 (March) 1937

involvement have been reported<sup>14</sup> In 4 cases bronchial asthma was complicated not only by pneumothorax but by subcutaneous emphysema<sup>15</sup>

In many cases the physical signs are those that might be expected However, Elliott<sup>15a</sup> asserted that there were no signs suggesting a pneumothorax in his patient, and McGuire<sup>16</sup> reported that the physical signs of a pneumothorax appeared only after some weeks Cyanosis is usually present, and orthopnea is not uncommon Patients are afebrile except with an associated bronchopneumonia<sup>17</sup> or pleural effusion,<sup>12c</sup> both of which complications have been reported only once Small amounts of non-fibrinous pleural fluid are often noted<sup>1</sup> There is no consistent abnormality of the pulse, respiration or blood pressure

Seven deaths from spontaneous pneumothorax complicating bronchial asthma have been reported<sup>18</sup> However, the condition is usually benign, the lung reexpanding without aspiration of pleural air within a few weeks One pneumothorax persisted for thirty years<sup>19</sup>

The role of pulmonary and interstitial emphysema in this type of pneumothorax will be considered later in the paper No association with pulmonary tuberculosis has been noted Chronic sinusitis and bronchitis do not appear to be predisposing factors In all adults with the condition the asthma had been present for several years

The blood count and the urine are normal and serologic tests for syphilis give negative

14 Faulkner and Wagner<sup>7</sup> Emerson and Beeler<sup>11a</sup> de Carvalho and da Silva Lacaz<sup>13</sup> Jeffrey and Marlatt<sup>33</sup>

15 (a) Elliott, R W Subcutaneous Emphysema and Pneumothorax in Bronchial Asthma, *Lancet* **1** 1104 (May 14) 1938 (b) Piaggio Blanco and Garcia Capurro<sup>2</sup> (c) Faulkner and Wagner<sup>7</sup> (d) Casiello<sup>10</sup>

16 McGuire, H H A Case of Pneumothorax Occurring in Bronchial Asthma, *Virginia M Monthly* **51** 167 (June) 1924

17 Kahn, I S Spontaneous Pneumothorax Due to Bronchial Asthma Case Report, *Texas State J Med* **28** 781 (March) 1933

18 (a) Rey, A J, Rey, J C, and Lértora, E Neumotórax espontáneo y asma, *Rev argent de tuberc* **5** 167 (July-Sept) 1939 (b) Nash, W G Surgical Emphysema in a Fatal Case of Influenza, *Brit M J* **1** 9 (Jan 4) 1919 (c) Fisher, R L Non-Tuberculous Spontaneous Pneumothorax, *Ann Int Med* **4** 1395 (May) 1931 (d) Austoni, M, and Marfori, L Considerazioni critiche su 33 casi di pneumotorace spontaneo, *Polichinico (sez med)* **46** 113 (March) 1939 (e) Faulkner and Wagner<sup>7</sup> (f) Emerson and Beeler<sup>11a</sup> (g) Gunther<sup>6</sup>

19 Mamini, C, and Alvarez, A A proposito de un caso de neumotórax total espontáneo benigno de 30 años de duración Recuperación de las funciones respiratorias por expansión parcial y eficiente del pulmón colapsado, *Prensa med argent* **22** 1411 (July 24) 1935

results, though leukocytosis may occur with the complications noted that cause fever

Roentgenograms may fail to reveal the pneumothorax<sup>2</sup> No roentgenographic evidence of mediastinal emphysema was noted in the previously reported cases

#### REPORT OF CASES

CASE 1—A 39 year old Spanish American man was admitted to the first medical division of Bellevue Hospital on April 7, 1939, with a chief complaint of increasing dyspnea during an asthmatic attack

*Past History*—He had had asthma for nine years, chiefly in the spring and summer, and had attended two allergy clinics in New York He had had many cutaneous tests, the results of which were apparently inconclusive Emotional upsets, strong odors and infections of the respiratory tract were named as factors in bringing on asthmatic attacks There was no history suggesting chronic sinusitis or pulmonary disease, and the system review revealed no other significant past history

*Family History*—There was no history of allergy or of any thoracic catastrophe suggesting a pneumothorax

*Present Illness*—Two weeks prior to the patient's admission an asthmatic attack developed following an infection of the upper respiratory tract The asthma persisted throughout this period, and he obtained only transient relief from frequent subcutaneous injections of epinephrine He had a steady severe cough Twelve hours before admission there was a sudden onset of dyspnea of a type that was definitely different from that accompanying asthmatic attacks He experienced no pain but came to the hospital when breathing seemed almost impossible

*Physical Examination*—The temperature was 100 F, the pulse rate 100, the respiratory rate 30 and the blood pressure 120 systolic and 75 diastolic The patient was a thin man who continued to be dyspneic, cyanotic and orthopneic after nasal administration of oxygen There was no evidence of infection of the nasopharynx or nasal sinuses The trachea was in the midline, and there was no subcutaneous emphysema The initial examination of the chest revealed only typical signs of bronchial asthma No difference between the right and the left side of the chest was noted Seven hours later the sibilant expiratory breath sounds had abated, and the breath sounds were greatly diminished on the right side The entire chest was hyperresonant, but particularly so on the right side There were a positive coin sound and lag on the right When the patient breathed deeply, many sibilant expiratory rales were heard over both sides of the chest, and there was only slight diminution of the intensity of the breath sounds on the right side

*Laboratory Studies*—The urine gave a 2 plus reaction for albumin but otherwise was normal The hemoglobin content of the blood was 16 Gm per hundred cubic centimeters The red cell count was 5,200,000 and the white cell count 12,400, with polymorphonuclear leukocytes 62 per cent, lymphocytes 30 per cent, monocytes 4 per cent and eosinophils 4 per cent The Wassermann reaction of the blood was negative

*Roentgen Examination*—Fluoroscopy several hours after the patient's admission to the hospital revealed an almost complete collapse of the right lung without marked mediastinal shift Roentgenograms taken two weeks later (after aspiration of air) showed a pneumothorax on the right side, with a 60 per cent collapse

of the lung, irregular adhesions at the base and a small amount of fluid in the costophrenic sinus

*Clinical Course*—The patient was treated with subcutaneous injections of epinephrine hydrochloride and nasal inhalations of oxygen. Several hours after he entered the hospital the pneumothorax became evident on physical examination. Twenty-four hours after his admission nonpleuritic costovertebral pain on the right side, vomiting and increased dyspnea made the aspiration of 300 cc of pleural air necessary. The intrapleural pressure was plus 3, plus 11 before the aspiration and minus 2, plus 2 afterward. The pain, dyspnea and vomiting persisted with diminishing severity for two weeks, and there was no striking relief from aspiration of pleural air. Five days after the patient's admission the initial pleural pressure was minus 6, plus 11, and after aspiration of 700 cc of air, minus 8, plus 8. At the end of two weeks there was almost complete expansion of the lung, with no further pulmonary symptoms. He was discharged on the fiftieth day of hospitalization, and although he was readmitted several times with the diagnosis of bronchial asthma and pulmonary emphysema, there was no recurrence of the pneumothorax.

*CASE 2*—A 33 year old American seaman was admitted to the first medical division of Bellevue Hospital Sept 8, 1938, with a history of several days of cough and asthma.

*Past History*—The patient had had a chronic cough throughout most of his adult life and had had asthmatic attacks for five to six years. On his first admission to the hospital, in 1935, the admission diagnosis was chronic bronchitis, malnutrition, fatty liver, chronic alcoholism and possible bronchial asthma. In 1936 he was admitted with the diagnosis of acute and chronic bronchitis and bronchial asthma. The asthma responded to oral administration of ephedrine sulfate. In 1938 a hemorrhoidectomy was postponed because of an exacerbation of bronchitis. There was no history of pulmonary tuberculosis, and a roentgenogram of the chest taken in 1935 revealed no sign of this disease. The patient said he had been a heavy drinker but that he had not indulged in alcoholic excesses in recent years. Except for gonorrhea at the age of 17, the system review revealed no significant past history.

*Present Illness*—Six days prior to admission the patient became increasingly short of breath during an asthmatic attack. He was gasping for air, and a physician gave him a hypodermic injection which temporarily relieved the dyspnea. Throughout the week, however, he became increasingly dyspneic, had constant anorexia and vomited on one occasion. There was no mention of pain prior to his admission.

*Physical Examination*—The temperature was 100.2 F, the pulse rate 120, the respiratory rate 30 and the blood pressure 120 systolic and 80 diastolic. The patient was a poorly nourished man appearing acutely and chronically ill, dyspneic, cyanotic and orthopneic. A postnasal discharge was noted. The chest was emphysematous, and prolonged high-pitched expiratory breath sounds and sibilant wheezes were heard bilaterally. The heart was normal except for the absence of an apical impulse in the usual location and the presence of an epigastric pulsation. Cardiac auscultation was unsatisfactory because of the loud breath sounds.

*Laboratory*—Urinalysis gave normal results. The white blood cell count was 8,850, with polymorphonuclear leukocytes 70 per cent, lymphocytes 28 per cent, monocytes 1 per cent and eosinophils 1 per cent.

*Clinical Course*—During the first twenty-four hours the clinical picture was that of bronchial asthma which failed to respond to the routine therapy for this condition. One observer confirmed the presence of signs of bronchial asthma bilaterally, and another noted that the wheezing was more pronounced on the left side of the chest. There was no tracheal deviation and no engorgement of the veins of the neck or dependent edema. The cyanosis noted on the patient's admission increased. Thirty-six hours after his admission the vital capacity was 1,500 cc. At about this time the chest began to "ache." The bronchospasm had not been relieved by epinephrine, ephedrine or ammonium chloride, and he was given a total of 0.6 Gm of sodium amytal over an eleven hour period. Because of extreme restlessness, a total of 20 cc of paraldehyde was given orally over a seven hour period. After this medication he insisted on walking about the ward but was apparently well oriented. Three hours later deep cyanosis was noted, the pulse rate was 84 per minute, and respiration was shallow, with a rate of 24 to 30 per minute. The pulse became feeble, and epinephrine and pentamethylene-tetrazol (metrazol) and also intravenous injections of 50 per cent dextrose solution were administered without effect. It was noted that the physical signs suggesting bronchospasm were abating and that the right hemithorax was poorly aerated. He was placed in a Drinker respirator. The cyanosis deepened, and he became comatose and failed to respond to noxious stimuli after two hours. After four hours in the respirator, sixty hours after admission, he died. Just prior to his death large amounts of grayish mucus were aspirated from the trachea. "This probably explains the markedly diminished aeration of the right lung" was one of the last notes made on the chart.

The temperature ranged from 97 to 100.2 F, the pulse rate from 90 to 100 and the respiratory rate from 24 to 30, except for terminal figures of 101 F, 120 and 60 respectively.

Permission for necropsy was not obtained.

Twenty-four hours after the death of the patient the routine roentgenogram of the chest taken on his admission was reported as showing "pneumothorax resulting in partial collapse of the right lung, minimal effusion in the costophrenic sinus, interstitial changes and fibrosis at the roots of both lungs, extending into the parenchyma, fusiform dilatation of the descending portion of the arch of the aorta."

#### COMMENT

In case 1 the diagnosis of spontaneous pneumothorax was not made during the asthmatic attack because insufficient importance was attached to the patient's statement that there was a sudden change in the character of his dyspnea. Also, as Laennec<sup>20</sup> has pointed out, the diagnosis of pneumothorax in an emphysematous person may be difficult because of the diffuse hyperresonance and distant breath sounds. As has been observed elsewhere,<sup>10</sup> sibilant asthmatic breath sounds were heard with great clarity over the pneumothorax.

In case 2 several observers noted physical signs that should have suggested the correct

20 Laennec, R. H. T. *De l'auscultation mediate*, Paris, J. A. Brosson & J. S. Chaude, 1819.

diagnosis. But the minds of those who saw the patient seemed closed to the possibility of a pneumothorax occurring during an asthmatic attack. It is possible, but unlikely, that death resulted from unwise administration of paraldehyde.<sup>21</sup> Had the diagnosis of pneumothorax been made, it is likely that appropriate therapy might have saved the patient. The use of the respirator was, of course, ill advised.

On few occasions is the physician's "index of suspicion" lower than when he is treating recurrent bronchial asthma. Roentgenograms cannot be ordered with every attack, and it was only by chance that in the second case a routine film taken on the patient's admission revealed the pneumothorax after his death. The large number of interesting medical and surgical methods of treating bronchial asthma tend to direct one's attention toward therapy rather than toward a consideration of a possible concomitant pathologic process. The clinical picture of an asthmatic patient with pneumothorax may be so alarming that the problem of relief of bronchospasm occupies the entire attention of the physician.

In both the cases reported here there was an associated chronic bronchitis and pulmonary emphysema. There is no evidence to suggest that the mechanism of the pneumothorax in the second case was any other than the usually accepted one of a rupture of the visceral pleura with a subsequent valvular action. In the first case the second manometric readings suggest an open pneumothorax, as in the case of Kahn.<sup>17</sup> At no time was the relief of symptoms from the aspiration of pleural air striking. The significance of this unusual feature of the pneumothorax in the first case will be discussed after a consideration of the newer knowledge of certain mediastinal air pathways.

Laennec<sup>20</sup> described interstitial emphysema, but until recent years the subject has received little attention. Discussing spontaneous pneumothorax in asthma, Hamman<sup>3c</sup> stated "one is justified in considering that the pneumothorax may be secondary to mediastinal emphysema." Elsewhere,<sup>22</sup> discussing spontaneous pneumothorax, he stated "It seems altogether likely that in most instances, if not in all, the air reaches the pleural cavity through the mediastinum. We have been accustomed to ascribe the escape of air to the rupture of emphysematous bullae and to minute tears produced

by the tug of adhesions. These explanations have never been altogether convincing, and I think that we must now at least entertain the possibility that the initial lesion of a spontaneous pneumothorax may be interstitial emphysema of the lung with an escape of air to the pleura through the mediastinum." Several features of the reported cases of spontaneous pneumothorax and asthma support Hamman's contention. It has been noted that subcutaneous emphysema of the neck may be associated with spontaneous pneumothorax and asthma, a fact which suggests the possibility of mediastinal pathways for air. (Seventeen collected cases of subcutaneous emphysema and bronchial asthma<sup>23</sup> make this condition appear somewhat more unusual than spontaneous pneumothorax as a complication of asthma. Experimentally, however, interstitial air tends to travel from the periphery to the mediastinum rather than to the pleural space<sup>22</sup>.)

Aspiration of the pleural air in this type of pneumothorax may not relieve the symptoms.<sup>23a</sup> This suggests that there may be some cause for cardiorespiratory embarrassment other than the compression of the lung. I recall seeing a patient with bilateral spontaneous pneumothorax with obliteration of the right radial pulse following tracheotomy. The extreme cyanosis and dyspnea were not relieved by aspiration of pleural air. Obliteration of the radial pulse has been reported to occur with spontaneous pneumothorax complicating bronchial asthma.<sup>7</sup> It is possible in these cases of bronchial asthma, as in the case of pneumothorax following tracheotomy, that aspiration of pleural air failed to relieve an associated mediastinal emphysema.

Pastorino,<sup>24</sup> writing on spontaneous pneumothorax and asthma in 1934, suspected the existence of bronchovascular pathways for air through the mediastinum. Their exact location was later demonstrated by Macklin. He introduced air under pressure into the terminal bronchi of cats and followed its course histologically. This experiment reproduced roughly the conditions in asthma when air is trapped under pressure in the smaller ramifications of the bronchial tree. He stated,<sup>25</sup> referring to air under pressure in the alveoli "there is a break through from the overdistended alveoli of the

23 Rosenberg, J, and Rosenberg, L. Subcutaneous Emphysema Complicating Bronchial Asthma, *Am J M Sc* **195** 682 (May) 1938

23a Harvey<sup>12b</sup> Elliott<sup>15a</sup> Case 1 of present report

24 Pastorino, A. Asma y enfisema, asma y neumotórax, *Rev de tuberc d Uruguay* **4**:256, 1934

25 Macklin, C C. Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum. Clinical Implications, *Arch Int Med* **64**:913 (Nov) 1939

21 Burstein, C L. The Hazard of Paraldehyde Administration. Clinical and Laboratory Studies, *J A M A* **121**:187 (Jan 16) 1943

22 Hamman, L. Spontaneous Mediastinal Emphysema, *Bull Johns Hopkins Hosp* **64**:1 (Jan) 1939



lung into the overlying perivascular sheaths multiple very small ruptures into the sheath system which overlie the finer ramifications of the pulmonary blood vessels." Once entrance has been gained to the perivascular sheaths, air can travel to the pleural space, to the mediastinum and neck, and even to the retroperitoneal space. Bronchoscopic studies during asthmatic attacks<sup>25a</sup> indicate that there is sufficient obstruction from bronchial constriction, edema and fibrin plugs to build up alveolar pressure. Macklin<sup>26</sup> stated that the pressures produced in his experiments were greater than might be encountered clinically. But the passage of air to the pleural space in accidental overinflation of the lung during intratracheal anesthesia<sup>27</sup> suggests the possibility of alveolar rupture and escape of air into the perivascular sheaths occurring in human beings as in experimental animals. The similarity of bronchial asthma complicated by pneumothorax and subcutaneous emphysema and the conditions observed in the experimental animals of Macklin also suggests that interstitial emphysema may occur as a complication of bronchial asthma. The similarity between cases of asthma thus complicated and cases in which there are pneumothorax and mediastinal emphysema secondary to a foreign body in a bronchus<sup>28</sup> is striking. In the latter cases it can be shown that the air enters the pleural space not through the visceral pleura but via the damaged alveoli.

However, the possibility that this type of pneumothorax may be secondary to rupture of a subpleural bleb cannot be dismissed, particularly since long-standing bronchial asthma and "asthmatic bronchitis" may be associated with pulmonary emphysema. But most authors state that spontaneous pneumothorax as a complication of bronchial asthma is rare in the presence of pulmonary emphysema.<sup>29</sup> The usual hypothesis advanced is that emphysematous tissue is more rigid than normal pulmonary tissue and resists compression. Cournand, Richards and

Maier<sup>30</sup> have reported on a patient in whom healthy tissue was compressed by a pneumothorax (artificial) whereas the emphysematous tissue was not. This fact makes spontaneous pneumothorax a particularly grave complication of pulmonary emphysema. Three autopsies on patients dying from spontaneous pneumothorax and bronchial asthma have been reported. Emerson and Beeler<sup>31a</sup> reported the presence of an associated pulmonary emphysema. Fornet<sup>32d</sup> described subpleural interstitial emphysema with lacerated alveoli. Auston and Marfori<sup>33d</sup> mentioned both pulmonary and interstitial emphysema with no demonstrable pleural lesion. A necropsy was not performed in Nash's fatal case,<sup>18b</sup> but he described a mediastinal resonance suggesting

"an escape of air from the lower trachea or bronchus into the mediastinum." Reports of 14 autopsies on persons dying during asthmatic attacks<sup>31</sup> mentioned "voluminous lungs" frequently but not interstitial emphysema. Macklin<sup>25</sup> stated that interstitial emphysema is rarely recognized without special intrabronchial fixation of the tissues. An unsuspected pneumothorax may easily be missed at autopsy. Rasmussen and Adams<sup>32</sup> expressed the belief that mediastinal and interstitial emphysema may be the cause of death in certain cases of bronchial asthma and have experimental evidence to support their contention. Macklin<sup>20</sup> stated that experimental interstitial emphysema may involve the opposite lung and that once a pneumothorax is established a contralateral pneumothorax may occur after a break through the thin mediastinal septum. This fact makes it unlikely that the relatively high incidence of bilateral pneumothorax in asthma previously referred to, is caused by bilateral "simultaneous rupture of bullae on the surface of the lungs," as has been suggested.<sup>33</sup> Fuchs<sup>12e</sup> reported a case of spontaneous pneumothorax occurring in an asthmatic patient after the intrabronchial instillation of iodized oil. Roentgenograms showed no oil in the pleural space, and the author suggested that the air

25a. Leggett<sup>8</sup> d'Abreu, A. L. Asthmatic Attack Studied Through Bronchoscope, *Lancet* **2** 421 (Oct 5) 1940

26. Macklin, C. C. Pneumothorax with Massive Collapse from Experimental Over-Inflation of the Lung Substance, *Canad M A J* **36** 414 (April) 1937

27. Heidrick, A. F., Adams, W. E., and Livingstone, H. M. Spontaneous Pneumothorax Following Positive Pressure Intratracheal Anesthesia. Report of a Case, *Arch Surg* **41** 61 (July) 1940

28. Fisher, J. H., and Macklin, C. C. Pulmonic Interstitial and Mediastinal Emphysema. Report of a Fatal Case in Which the Emphysema Occurred in a Child as a Result of the Aspiration of Peanut Fragments, *Am J Dis Child* **60** 102 (July) 1940

29. Castex and Mazzei<sup>4</sup> Faulkner and Wagner<sup>7</sup> Casiello<sup>10</sup> Rey, Rey and Lertora<sup>18a</sup> Pastorino<sup>24</sup>

30. Cournand, A., Richards, D. W., and Maier, H. C. Pulmonary Insufficiency, *Am Rev Tuberc* **44** 272 (Sept) 1941

31. Craige, B. Fatal Bronchial Asthma. Report of Seven Cases, *Arch Int Med* **67** 399 (Feb) 1941. Bases, L., and Kurtin, A. Prevention of Death in Status Asthmaticus. Value of Bronchoscopy, *Arch Otolaryng* **36** 79 (July) 1942

32. Rasmussen, R. A., and Adams, W. E. Experimental Production of Emphysema, *Arch Int Med* **70** 379 (Sept) 1942

33. Jeffrey, G. S., and Marlatt, D. C. Simultaneous Bilateral Spontaneous Pneumothorax Complicating Bronchial Asthma, *Canad M A J* **39** 171 (Aug) 1938



escaped from distended bronchioles rather than through the surface of the visceral pleura

A concomitant mediastinal and interstitial emphysema may explain the extreme degree of cardiorespiratory embarrassment in cases of spontaneous pneumothorax and bronchial asthma when the symptoms persist after aspiration of pleural air and relief of bronchospasm. Macklin<sup>25</sup> stated that air in the perivascular sheaths acts as "an air vise" and may interfere with both the arterial and the venous blood supply with resulting failure of the right side of the heart. Ballon and Francis,<sup>34</sup> in conclusions drawn from both clinical and experimental material, stated that mediastinal air not only may cause cardiac tamponade but may compress even the axillary and femoral vessels. They reported edema of the trachea and bronchi in mediastinal emphysema, a fact which would make mediastinal emphysema a particularly disastrous complication of bronchial asthma.

Most authors favor conservative management of bronchial asthma complicated by spontaneous pneumothorax. Aspiration of pleural air is usually not necessary. If there is evidence of mediastinal or interstitial emphysema, it may be advisable to maintain the pneumothorax to stop

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34 Ballon, H. C., and Francis, B. E. Consequences of Variations in Mediastinal Pressure. Mediastinal and Subcutaneous Emphysema, *Arch Surg* **19** 1627 (Dec) 1929

the leak of air rather than to aspirate pleural air.<sup>35</sup> Although the administration of morphine to patients with bronchial asthma is usually not condoned, it may be necessary to use this drug to stop a cough that is building up intra-alveolar pressure. No definite outline of therapy can be given, since individual cases vary greatly in respect to associated pulmonary and interstitial emphysema, bronchial infection and numerous other factors. Although mediastinal emphysema is usually a benign condition, it should be noted that surgical release of mediastinal air may be necessary.<sup>25</sup> Surgical treatment was not suggested by any of the authors writing on spontaneous pneumothorax complicating bronchial asthma, but it might be indicated for a moribund patient. The use of dextrose solution intrapleurally has been suggested to prevent the frequent recurrence of spontaneous pneumothorax in asthmatic persons.<sup>12b</sup>

#### SUMMARY

Spontaneous pneumothorax occurred as a complication of bronchial asthma in 2 cases. This is a potentially fatal complication of bronchial asthma. Its diagnosis is extremely difficult in certain cases. This complication should be considered in every case of intractable or atypical asthma. Spontaneous pneumothorax and bronchial asthma are probably sometimes associated with mediastinal and interstitial emphysema.

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35 Harvey<sup>12b</sup> Macklin<sup>25</sup>

# NUTRITIONAL PROBLEMS PRESENTED BY A PATIENT WITH EXTENSIVE JEJUNOILEITIS

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Granulomatous jejunoileitis and its clinical manifestations have been well described,<sup>1</sup> but less attention has been devoted to some of the nutritional problems which may attend this disease. The nature of these problems is well exemplified by the case of a patient recently, under our observation. Not only were the functions of his small intestine impaired by an extensive granulomatous process, but he suffered from severe hypoproteinemia, partly induced by a period of semistarvation in an open lifeboat. This report presents the results of various therapeutic measures which were evaluated on the basis of the patient's clinical course, daily nitrogen balances and other laboratory data obtained over a period of forty-two weeks.

## REPORT OF A CASE

R D, a 23 year old white American man, was admitted to the Evans Memorial Hospital on July 28, 1942, with the chief complaint of diarrhea of three months' duration. His past history was noncontributory. At no time did he have any gastrointestinal disturbance. His weight, however, which six years previously had been 180 pounds (81.6 Kg), dropped to 140 pounds (63.5 Kg) in the three to four years immediately preceding entry to the hospital.

Thirteen weeks before the patient was admitted to the hospital, the ship on which he was serving as a mess boy was torpedoed. Subsequently he was exposed in an open lifeboat for eight days and had to subsist on small rations of chocolate, malted milk tablets, biscuits and water. During the last two days of this ordeal, his ankles began to swell, although in none of the other men in the lifeboat did this condition develop. After the group was rescued, the patient had his first bowel movement in eight days. He was thereafter received at a small hospital on the eastern coast of the United States, where he remained for two months. For the first five weeks of his course there he had four to five small, watery bowel movements daily. These contained a small amount of blood on rare occasions. Thereafter the movements decreased to two a day. He was treated with a limited dietary intake and orally administered vitamins and received one blood transfusion. During these two months he lost approximately 14 pounds (6.4 Kg) in weight.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

1 (a) Crohn, B B, and Yunch, A M. Ileojejun-itis, *Ann Surg* **113** 371-380 (March) 1941. (b) Sussman, M L, and Wachtel, E. Granulomatous Jejuno-Ileitis, *Radiology* **39** 48-53 (July) 1942.

The patient was transferred to a Marine hospital on June 17, 1942, where he was found to be emaciated and dehydrated. Pitting edema of the ankles extended one third of the way to the knees. The tongue was smooth but not sore. During the first seventeen days, a septic type of fever (the temperature rising to 102 F) was present, but thereafter the course was afebrile. Laboratory data on his admission to the hospital were as follows: red blood cell count, 1,200,000, hemoglobin content, 54 per cent, hematocrit value, 22 per cent, and reticulocyte count, 14 per cent. A halometer reading showed the red blood cells to average 84 microns in diameter. The white blood cell count was 3,200 with a differential count of 33 per cent polymorphonuclear leukocytes, 65 per cent lymphocytes and 2 per cent eosinophils. The icterus index was 2 and the sedimentation rate was 6 mm in one hour (normal). The serum total protein content was 4.85 Gm per hundred cubic centimeters, with 2.34 Gm of albumin and 2.51 Gm of globulin. The urine was normal except for a trace of albumin. Gastric analysis showed absence of free hydrochloric acid after stimulation with histamine. There were no ova or parasites in the stools, fat was present, but the exact amount was not determined.

The patient was considered to have sprue or pernicious anemia and was therefore given daily parenteral injections of liver extract and vitamin B complex. Diarrhea stopped on the second day of this therapy. The red blood cell count began to rise, and the reticulocyte count reached 12 per cent after ten days. After the red blood cell count reached 3,000,000, the patient began to have diarrhea again, with loss of weight. After three blood transfusions, some improvement occurred and the red blood cell count rose to 4,300,000 with a hemoglobin content of 78 per cent. The reticulocyte count gradually decreased to 13 per cent. The total white blood cell count and the differential count returned to normal values within two weeks. The serum total protein content decreased slightly to 4.7 Gm per hundred cubic centimeters, with albumin 2.15 Gm and globulin 2.55 Gm. An oral dextrose tolerance test showed the fasting blood sugar level to be 49 mg per hundred cubic centimeters, one-half hour after ingestion of 100 Gm of dextrose the level was 106 mg, at three hours, 67 mg, and at four hours, 50 mg. Roentgenograms of the skull, sternum, pelvis and chest revealed no abnormalities. Gastrointestinal roentgen studies showed the stomach to be normal. In six hours the barium sulfate had reached the sigmoid region, but a considerable amount of it was retained in the ileum, the mucosal pattern of which was suggestive of ulcerative enteritis. A roentgenogram after a barium enema revealed normal conditions.

On July 28 the patient was transferred to the Evans Memorial Hospital for further study. He was a tall, well developed but moderately emaciated young man who weighed only 113 pounds (51.3 Kg). The eyes, ears, nose and throat were not unusual. The tongue was normal. The lungs and heart were within normal

limits. The blood pressure was 124 systolic and 76 diastolic. There was moderate abdominal distention with tympany, tenderness was not present. The liver and spleen were not felt. There was clubbing of the fingers and toes. Slight pitting edema of the ankles was present. There were several external hemorrhoids.

The laboratory data on admission were: Hinton reaction of the blood, negative; red blood cell count, 4,250,000; hemoglobin content, 12 Gm; hematocrit value, 38.8 per cent; mean corpuscular volume, 91.3 cubic microns; mean corpuscular hemoglobin concentration, 31.2 per cent; mean corpuscular hemoglobin content, 28.3 micromicrograms; and reticulocyte count, 0.2 per cent. The white blood cell count was 6,200, with a differential count of 72 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes and 3 per cent monocytes. The urine was normal. The nonprotein nitrogen content of the blood was 26 mg per hundred cubic centimeters. The fasting blood sugar level was 80 mg and the serum total protein level 3.75 Gm per hundred cubic centimeters. The corrected sedimentation rate (Wintrobe) was 0.1 mm per minute. The stools were watery and light brown, and a guaiac test elicited a negative reaction.

Roentgen ray studies of the gastrointestinal tract revealed a normal stomach. The duodenum was somewhat dilated, and localized areas of dilatation with puddling of the barium and thickening of the mucosal folds were demonstrated in the upper portion of the jejunum. The lower part of the jejunum and the ileum exhibited fixed narrowing of the intestinal lumen, irregular and ragged mucosal markings and sharply localized round areas of dilatation (fig 1). Intubation study of the upper portion of the jejunum demonstrated an abnormal motility pattern with low tone and frequent large waves tending to occlude the jejunal lumen. Gastric analysis on two occasions showed the presence of free hydrochloric acid in the fasting specimens. The result of an intravenous hippuric acid test was normal, 0.9 Gm being excreted in one hour. The prothrombin content of the blood was 100 per cent. The cholesterol contents of the blood were 105 and 115 mg per hundred cubic centimeters and the cholesterol ester contents 33 and 37 per cent. The alkaline phosphatase level was 3 units (King and Armstrong). The serum calcium levels were 8.0 and 8.2 mg per hundred cubic centimeters, the inorganic phosphorus levels, 3.5 and 3.8 mg, the diastase activity, 41 and 43 units (Somogyi), and the lipase activity, 0.93 units (Crandall and Cherry). The urinary diastase activity varied between 4 and 8 units (Wohlgemuth). The basal metabolic rate was -10 per cent on one occasion and -5 per cent on another. An electrocardiogram revealed normal conditions. The tuberculin test elicited negative reactions in dilutions of 1:10,000 and 1:1,000. Guinea pig inoculation with fecal material proved negative for tubercle bacilli.

**Clinical Course**—The patient was afebrile and was allowed to walk about the ward as desired. His diet consisted of 300 to 400 Gm of carbohydrate and about 100 Gm each of protein and fat, amounting to an average daily intake of 2,500 to 3,000 calories. He received daily intramuscular injections of liver extract, later these were given twice weekly. He also took moderately large amounts of thiamine hydrochloride, nicotinic acid, riboflavin and vitamins A and D orally.

During the first month the patient showed no significant improvement, although the stools became semi-formed and there was a slight gain in weight. However, the total proteins of the serum continued to decrease,

reaching the exceptionally low level of 3.2 Gm per hundred cubic centimeters with an albumin fraction of 1.7 Gm. Coincident with these changes there was a definite increase in the edema of the legs. It was evident that measures had to be taken to increase the blood proteins. Transfusions of blood plasma were considered, but the scarcity of plasma for civilian use, the tremendous amounts that would be required and the expense involved in such therapy prohibited this type of treatment. A considerable increase in dietary protein was incompatible with the patient's appetite, and it was considered questionable whether his abnormal intestine could handle an excess intake of protein. Since experimental<sup>2</sup> and clinical<sup>3</sup> reports have proved the efficacy of amino acids and protein hydrolysates administered parenterally and orally in maintaining a positive nitro-

2 (a) Nielsen, E. K., Gerber, L. P., and Corley, R. C. Retention of the Nitrogen of Amino Acids Administered Singly or in Mixtures to Dogs Fed Diets Low in Protein, *Am J Physiol* **126**:215-222 (June) 1939. (b) Nielsen, E. K., and Corley, R. C. Retention of the Nitrogen of Mixtures of Amino Acids Administered to Rats Fed Diets Low in Protein, *ibid* **126**:223-228 (June) 1939. (c) Mueller, A. J., Kemmerer, K. S., Cox, W. M., Jr., and Barnes, S. T. The Effect of Casein and a Casein Digest on Growth and Serum Protein Regeneration, *J Biol Chem* **134**:573-583 (July) 1940. (d) Madden, S. C., Zeldis, L. J., Hengerer, A. D., Miller, L. L., Rowe, A. P., Turner, A. P., and Whipple, G. H. Casein Digests Parenterally Utilized to Form Blood Plasma Protein, *J Exper Med* **73**:727-743 (June) 1941. (e) Clark, D. E., Brunschwig, A., and Corbin, N. Utilization of Parenterally Administered Casein Digest for Synthesis of Proteins, *Proc Soc Exper Biol & Med* **49**:282-285 (Feb) 1942. (f) Elman, R., Sachar, L. A., Horwitz, A., and Wolff, H. Regeneration of Serum Albumin with Hydrolyzed Protein in Chronic Hypoproteinemia Produced by Diet, *Arch Surg* **44**:1064-1070 (June) 1942.

3 Shohl, A. T., Butler, A. M., Blackfan, K. D., and MacLachlan, E. Nitrogen Metabolism During the Oral and Parenteral Administration of the Amino Acids of Hydrolyzed Casein, *J Pediat* **15**:469-475 (Oct) 1939. Farr, L. E., Emerson, K., and Futcher, P. H. The Comparative Nutritive Efficiency of Intravenous Amino Acid and Dietary Protein in Children with the Nephrotic Syndrome, *ibid* **17**:595-614 (Nov) 1940. Elman, R. Parenteral Replacement of Protein with the Amino Acids of Hydrolyzed Casein, *Ann Surg* **112**:594-602 (Oct) 1940. Messinger, W. J. Serum Protein Regeneration Following Use of Amino Acids in Nephritis (Nephrotic Stage), *Proc Soc Exper Biol & Med* **47**:281-284 (June) 1941. Brunschwig, A., Clark, D. E., and Corbin, N. Postoperative Nitrogen Loss and Studies on Parenteral Nitrogen Nutrition by Means of Casein Digest, *Ann Surg* **115**:1091-1102 (June) 1942. Altshuler, S. S., Hensel, H. M., Hecht, P., and Pursley, R. Maintenance of Nitrogen Equilibrium by Intravenous Administration of Amino Acids, *Arch Int Med* **70**:749-762 (Nov) 1942. Altshuler, S. S., Sahyun, M., Schneider, H., and Satriano, D. Clinical Use of Amino Acids for the Maintenance of Nitrogen Equilibrium, *J A M A* **121**:163-167 (Jan 16) 1943. Mueller, A. J., Fickas, D., and Cox, W. M., Jr. Minimum Maintenance Requirement of an Enzymic Casein Hydrolysate, *Bull Johns Hopkins Hosp* **72**:110-115 (Feb) 1943. Elman, R. The Oral Use of the Amino Acids of Hydrolyzed Casein (Amigen) in Surgical Patients, *Am. J Digest Dis* **10**:48-50 (Feb) 1943.

gen balance and in some instances causing a regeneration of serum albumin, the patient was placed on a regimen of oral amino acids. The preparation used<sup>4</sup> was sufficiently concentrated so that he could take from 60 to 80 Gm of amino acids daily. Another consideration which prompted the use of oral amino acids in preference to proteins was the fact that only the upper third of the small intestine was presumably capable of absorbing foods adequately. Under such circumstances, it seemed reasonable to administer a predigested form of protein material which would be available for absorption immediately on entering the duodenum and upper part of the jejunum.

In order to determine accurately the efficacy of administration of amino acids, it was necessary to carry out nitrogen balance studies.<sup>5</sup> As can be seen from figure 2, the exhibition of orally administered amino acids was followed by an increase in the positive nitro-

after the loss of the edema fluid, and it became evident that although he was still in positive nitrogen balance there was little further improvement in his clinical course.

Analyses of his stools revealed that the daily excretion of nitrogen was only slightly above the upper limits of normal (table 1). That the amino acids were being utilized as well as absorbed was shown by analysis of the urine during a four day period, the excretion of amino acid nitrogen was small (table 2).

Steatorrhea was present, but the total amount of fat excreted, with the resultant caloric loss, was not significant (table 1). Since the lipase content of the duodenal juices was normal both in the fasting state and after pancreatic stimulation with acetylbetamethylcholine chloride (mecholy) the moderate fecal loss of lipids was ascribed principally to curtailment in the absorbing surface of the small intestine. That absorption of fat-soluble vitamins occurred, although less than normal, was demonstrated by vitamin A tolerance tests, 250,000 U S P units of vitamin A being used as the test dose (fig 3). The fasting serum carotene values were also below normal, varying between 0.025 and 0.060 mg per hundred cubic centimeters.

Oral dextrose tolerance tests showed that the patient was able to absorb dextrose rapidly from the small intestine, and the result of an intravenous dextrose tolerance test was within normal limits (fig 4). Staining the stool with solution of iodine did not reveal an abnormal amount of undigested starch particles. However, on two successive occasions the pancreatic amylase was found to be 22.2 and 8.8 units (as grams of maltose) when the patient was fasting and 32.2 and 11.3 units after acetylbetamethylcholine chloride (mecholy) was injected. The deficiency of pancreatic amylase suggested that the carbohydrates of more complex nature were probably not hydrolyzed sufficiently to permit normal absorption from the limited surface area of the non-diseased portions of small intestine. In order to increase the hydrolysis of starch in the stomach and upper part of the small intestine, a fungous amylase concentrate<sup>6</sup> was given in a dosage of 2 Gm with each meal. With each dose of this concentrate 4 Gm of calcium carbonate was taken in order to decrease the gastric acidity, the optimum  $pH$  for the concentrate being between 5 and 6. Since the combination of orally administered amino acids and concentrated amylase produced nausea and a consequent decrease in food intake, the amino acids were discontinued after two weeks. With the amylase concentrate alone, however, progressive improvement was clearly evident (fig 2).

During his thirty-eighth week in the hospital the patient was given amino acids<sup>7</sup> intravenously equivalent to 6 Gm of nitrogen daily in order to determine whether an increase in the positive nitrogen balance would occur while he was still taking the concentrated amylase. However, there was no increase in nitrogen retention on this regimen.

An interesting observation was made in regard to the stool culture on Sabouraud's medium. Throughout the course prior to administration of the concentrated amylase, the stool cultures (and on one occasion a



Fig 1—Roentgenologic appearance of the small intestine. A and B, one hour roentgenograms taken on Dec 11, 1942 and May 4, 1943, showing persistence of abnormalities. C, two hour roentgenogram taken on July 3, 1943, and D, three hour roentgenogram taken on Dec 11, 1942, showing extensive distribution of abnormalities.

gen balance, with a rise in the serum total proteins to 4.94 Gm per hundred cubic centimeters. However, this level was not maintained, and there was a gradual decline of the proteins to approximately 4 Gm per hundred cubic centimeters. The peripheral edema disappeared three months after the start of the amino acid therapy. The patient's weight remained stationary long

4 Amino acids for oral use, derived from the enzymatic hydrolysis of casein, were furnished by Frederick Stearns & Company, Detroit.

5 The methods are described in the appendix.

6 The amylase concentrate (Neozyme) was supplied by Frederick Stearns & Company, Detroit. It is prepared from a selected species of the *Aspergillus oryzae* group. One 0.65 Gm tablet will convert approximately 63 Gm of potato starch into absorbable sugars at the end of five hours (in vitro).

7 The amino acids for parenteral use were furnished by Frederick Stearns & Company, Detroit.

culture of jejunal contents) showed a growth of *Parasaccharomyces G* (*Monilia albicans*) When stool cultures were made during the second week of therapy with the amylase concentrate, the cultures showed no growth and repeated cultures thereafter did not contain yeasts However, cultures made five days after discontinuance of use of the concentrate again yielded *Parasaccharomyces G*

COMMENT

Granulomatous jejunoileitis is an inflammatory disease of the small intestine of unknown cause It appears to be closely related to regional enteritis but is characterized by a diffuse involvement of the jejunum as well as the ileum The

Yunich<sup>1a</sup> were able to segregate 17 examples of ileojejunitis

The case we have reported fits well into the group of cases designated as jejunoileitis The diarrhea, anorexia, loss of weight and low grade febrile course exhibited are among the outstanding symptoms of this disease However, abdominal pain and cramps, prominent in the typical case, were not present Clubbing of the fingers, frequently found in chronic malfunction of the intestine, was another feature exhibited by this patient The severe hyperchromic macrocytic anemia, possibly due to a lack of extrinsic

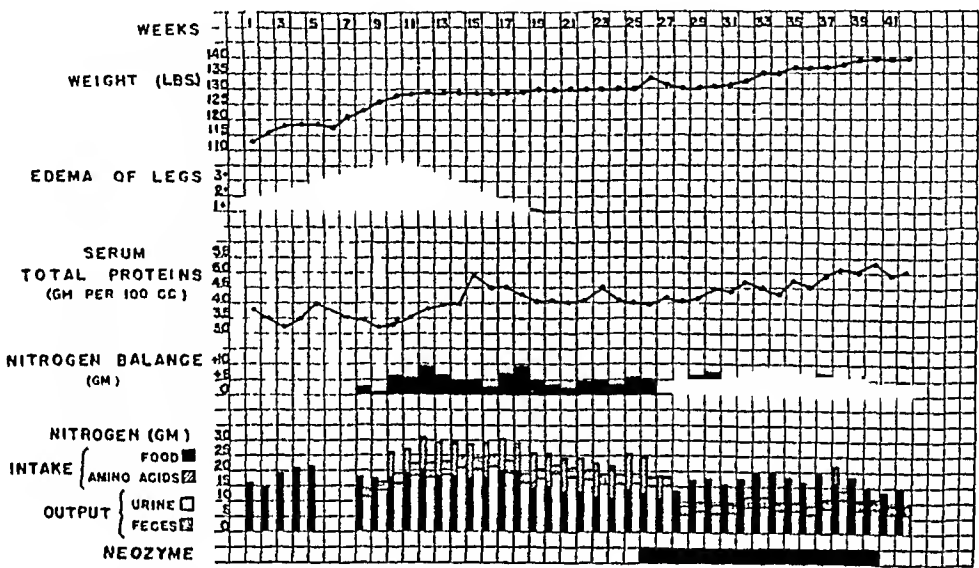


Fig 2—Clinical course and weekly nitrogen balances The weekly nitrogen balances were obtained by averaging the daily balances determined during each week

TABLE 1—Analyses of Feces for Nitrogen and Lipid Content

	Wet Feces, Gm	Dry Feces, Gm	Fecal Nitrogen, Gm	Fecal Fat, Gm	Fat in Dry Feces, per Cent	Fat in Det., Gm	Dietary Fat Excreted per Cent
Period I Sept 25, 26, 27, 1942	293.3	59.1	3.3	22.1	37	90	24
Period II Oct 14, 15, 16, 1942	309.9	63.9	4.0	19.5	30	99	22
Period III Nov 29, 30, and Dec 1, 1942	229.0	44.0	2.75	14.4	32	90	16
Period IV April 30 and May 1, 2, 1943	236.4	54.8	5.4	18.3	33	130	14
Normal values (average upper limits)	170.0	45.0	3.0		20		10

TABLE 2—Daily Urinary Excretion of Total Nitrogen, Urea Nitrogen and Amino Acid Nitrogen

Date	Total Urinary Nitrogen per 24 Hours, Gm	Urea Nitrogen				Amino Acid Nitrogen	
		Mg per 100 Cc	24 Hour Total, Gm	Per Cent of Total Urinary Nitrogen	Mg per 100 Cc	24 Hour Total Gm	
11/27/42	14.28	728.2	9.46	66	18.0	0.23	
11/28/42	14.88	666.6	10.66	71	17.0	0.27	
11/29/42	18.94	787.0	15.16	75	20.2	0.36	
11/30/42	20.00	702.0	14.04	70	20.2	0.44	

first extensive reports of a series of such cases were made by Crohn and Yunich<sup>1a</sup> and Sussman and Wachtel<sup>1b</sup> Out of their experience with 200 cases of regional ileitis, Crohn and

factor, responded well to parenteral injections of liver extract Gastric achlorhydria was present during the acute stage of the disease, but gastric analyses later showed free hydrochloric acid in the fasting contents The roentgenologic appearance of the gastrointestinal tract showed a striking similarity to that described in the reported cases Although the patient made a pronounced clinical improvement, the abnormalities evident in the small intestinal pattern showed no significant changes during a year of observation

Several features exhibited by this case suggested sprue, but it was excluded on the basis of the roentgenologic observations, the intestinal motility records, the dextrose tolerance tests, the

vitamin A tolerance tests, the mild steatorrhea, the normal prothrombin levels of the blood and the clinical course. On the other hand, it is not impossible that a spruelike process was superimposed on the granulomatous disease at the time of the patient's entry to the Marine hospital.

The severe hypoproteinemia was undoubtedly aggravated by the eight day period of starvation, the prolonged diarrhea and the inadequate absorption of various components of the diet. The

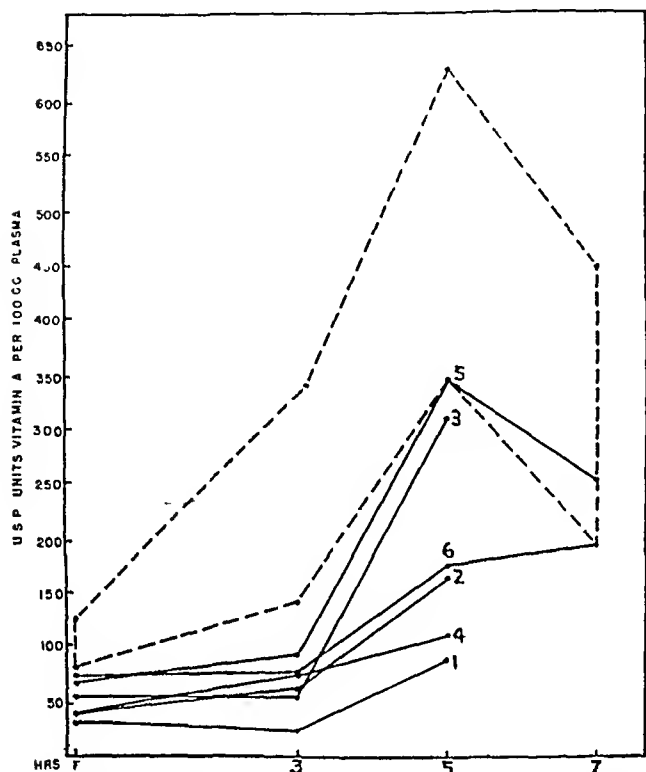


Fig 3—Vitamin A tolerance tests. The figure formed by the dotted lines encloses the normal values. The solid lines indicate results of tests on the patient: 1, on July 30, 1942, 2, on Sept 17, 1942, 3, on Dec 15, 1942, 4, on May 18, 1943, 5, on June 5, 1943, 6, on June 20, 1943.

oral administration of large amounts of amino acids in addition to the regular diet was instrumental in creating a significant positive nitrogen balance and resulted in a rise in the serum albumin with a partial correction of the hypoproteinemia. The large dose of hydrolyzed protein necessary to cause a regeneration of serum albumin has been demonstrated by Elman and associates<sup>2f</sup> in dogs rendered hypoproteinemic by protein-deficient diets, 96.5 per cent of the nitrogen retained by the animals was utilized for the replenishment of the tissue proteins, while only about 3.5 per cent could be accounted for in the replenishment of serum albumin.

In spite of a diet apparently adequate in carbohydrate, fat and protein, the patient reached a state where there was no further increase in the serum proteins, even though administration of amino acids was continued. It seemed that although the amino acids were being absorbed

from the gastrointestinal tract, they were possibly being deaminated and the non-nitrogenous residue used to furnish energy to the body. Since the patient was not gaining weight, this was fairly good evidence that the non-nitrogenous portion of the molecule was not being stored either as glycogen or as fat.

One reason that the patient's dietary intake was insufficient to take care of his metabolic requirements became apparent when an analysis of the duodenal juices revealed a deficiency of pancreatic amylase. Thus many of the more complex carbohydrates in his diet presumably were not hydrolyzed to dextrose in the upper part of the small intestine, and innumerable calories were lost in this manner. That deficiency of pancreatic amylase can exist without a simultaneous deficiency of pancreatic lipase or trypsin has been pointed out by Andersen,<sup>8</sup> who found that infants with chronic diarrhea exhibit this phenomenon. Furthermore, it has been shown experimentally by Grossman, Greengard and Ivy<sup>9</sup> that the type of diet influences the enzyme makeup of the pancreas and its secretion. That this patient's disease of the small intestine conditioned the insufficiency of pancreatic amylase is possible but is not supported by any evidence.

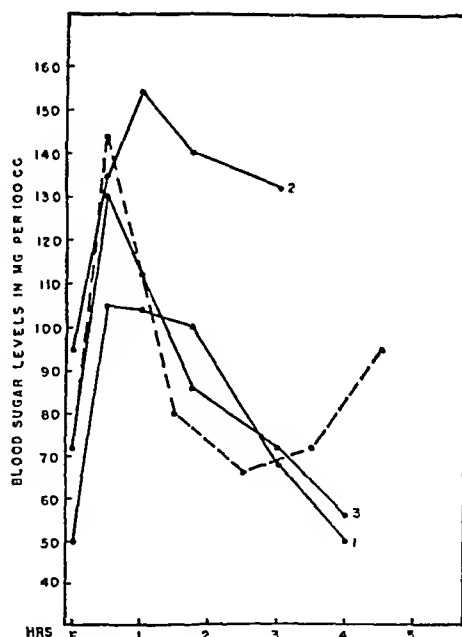


Fig 4—Dextrose tolerance tests. The solid lines represent results of oral tests: 1, on July 23, 1942, 2, on Aug 5, 1942, 3, on June 4, 1943. The dotted line represents results of an intravenous test on Dec 18, 1942.

The response to the amylase concentrate was striking. The immediate effect noticed was a de-

8 Andersen, D. H. Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, *Am J Dis Child* **63** 643-658 (April) 1943.

9 Grossman, M. I., Greengard, H., and Ivy, A. C. The Effect of Dietary Composition on Pancreatic Enzymes, *Am J Physiol* **138** 676-682 (March) 1943.



crease in abdominal distention and flatus. The appetite improved, more nitrogen was retained, serum albumin and total protein increased and a considerable gain in weight occurred. The disappearance of *Monilia albicans* (*Parasaccharomyces G*) from the stools while the patient was taking the amylase concentrate also suggests that the carbohydrates were broken down and absorbed rather than allowed to ferment in the intestine and so provide a favorable substrate for growth of these yeasts.

Serum vitamin A determinations showed extremely low fasting levels, but a progressive rise in these levels occurred after vitamin A was administered daily. The rise in the serum vitamin A level following a single large dose of vitamin A by mouth indicated that this fat-soluble vitamin could be absorbed even from an extensively damaged small intestine. On the other hand, the vitamin A tolerance tests yielded results which were definitely below the normal range (fig 4), which is somewhat at variance with the results of Adlersberg and Sobotka,<sup>10</sup> who found that the average value of vitamin A tolerance tests carried out in 5 cases of jejunoileitis tended to fall within the normal range.

#### SUMMARY

A patient with extensive granulomatous jejunoileitis and pronounced hypoproteinemia was studied and the following observations made:

1 A deficiency in pancreatic amylase complicated the intestinal disease.

2 A positive nitrogen balance was easily established, but the hypoproteinemia and the weight responded only moderately to a high oral intake of proteins and amino acids.

3 Oral administration of a concentrated amylase was followed by a gain in weight and an increase in serum proteins, presumably by an increase in the breakdown and absorption of car-

bohydrates, which prevented the use of amino acids as a source of bodily energy.

4 The administration of the amylase appeared to inhibit the growth of *Monilia albicans* in the stools.

Dr Chester Keefer and Dr Richard Johnson made many suggestions regarding this study.

#### APPENDIX

*Methods*—The food consumed by the patient was weighed by the dietitian and the protein, fat, carbohydrate and caloric value calculated from standard food tables. Twenty-four hour specimens of urine were collected daily and analyzed for total nitrogen. On several occasions specimens of urine were analyzed for amino acid nitrogen (Sahyun)<sup>11</sup> and urea nitrogen.

The stools were collected during four three day periods. The total lipid content was determined by acidifying and drying the total fecal output for a three day period. The dried feces were then powdered, and a 10 Gm aliquot was extracted with ether in a Soxhlet apparatus and reextracted with purified benzine. The dried stools were also analyzed for total nitrogen content (Kjeldahl).

Determinations of the total serum proteins were made three times a week by the falling drop method, and occasionally these results were checked by the Kjeldahl method. Amino acid nitrogen levels of the blood were determined twice weekly according to the method of Sahyun.<sup>11</sup>

Vitamin A and carotene in the serum were determined according to the method of May and associates.<sup>12</sup>

The duodenal contents were collected by the method of Ågren and Lagerlof.<sup>13</sup> The pancreatic amylase was determined according to the method of the same authors, and the pancreatic lipase, by the method of Crandall and Cherry.<sup>14</sup>

11 Sahyun, M. The Determination of Amino Acid Nitrogen in the Blood and Urine. A Rapid Colorimetric Method, *J Lab & Clin Med* **24** 548-553 (Feb) 1939.

12 May, C D, Blackfan, K D, McCreary, J F, and Allen, F H, Jr. Clinical Studies of Vitamin A in Infants and Children, *Am J Dis Child* **59** 1167-1184 (June) 1940.

13 Ågren, G, and Lagerlof, H. The Pancreatic Secretion in Man After Intravenous Administration of Secretin, *Acta med Scandinav* **90** 1-29, 1936.

14 Crandall, L A, Jr, and Cherry, I S. Studies on the Specificity and Behavior of Blood and Tissue Lipases, *Proc Soc Exper Biol & Med* **28** 570-572 (March) 1931.

10 Adlersberg, D, and Sobotka, H. Fat and Vitamin A Absorption in Sprue and Jejuno-Ileitis, *Gastroenterology* **1** 357-365 (April) 1943.

# LATE CEREBRAL SEQUELAE OF RHEUMATIC FEVER

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Until recently, rheumatic fever has been viewed as a disease taking place within a short period. The newer concepts, however, emphasize that the rheumatic infection may endure through the entire life of the patient.

Mental symptoms during acute rheumatic fever have been observed since the days of Benjamin Rush, founder of American psychiatry.<sup>1</sup>

Mental disease occurring within a period of several months following the acute stage, as the result of rheumatic cerebral involvement, has been described by Winkelman and Eckel.<sup>2</sup> A woman aged 33 had rheumatic fever. She recovered sufficiently to be able to do light house work. Several months later she began to have ideas of persecution, visual hallucinations and suicidal tendencies. When she died, shortly afterward, microscopic examination of the brain revealed proliferative endarteritis of the small cortical vessels and minute areas of partial and complete softening in the gray matter.

More recent neuropathologic studies<sup>3</sup> have directed attention to the fact that rheumatic involvement of the brain causing mental illness may occur many years after the acute stage of

rheumatic fever, at a time when the person is otherwise enjoying good physical health.

This viewpoint had its inception in postmortem observations. In the necropsy service of the Central State Hospital, in Indianapolis, it was noted that patients with rheumatic lesions of the cardiac valves not infrequently had concomitant gross or microscopic changes in the brain and in other organs which, in the absence of other possible causative factors such as syphilis or arteriosclerosis, were interpreted as rheumatic alterations.

Several questions then presented themselves. First, what is the incidence of rheumatic infection among inmates of mental institutions? Secondly, what are the changes in the brain tissues of rheumatic patients who ultimately find their way into state hospitals? Thirdly, what are the psychiatric symptoms of these patients?

## INCIDENCE OF RHEUMATIC FEVER AMONG PATIENTS WITH MENTAL DISEASE

An infallible sign of rheumatic fever in its inactive stage is rheumatic heart disease. In a group of 500 consecutive and unselected necropsies which I made on patients with mental disease, rheumatic cardiovalvular changes were noted in 4.4 per cent of the subjects. There was an additional 0.6 per cent of patients with rheumatic valvular lesions who had had positive reactions for syphilis. This made a total of 5 per cent of patients having rheumatic cardiac disease.

The figure of 5 per cent may be considered as representative of the prevalence of rheumatic heart disease in the population of the average mental disease hospital located in the same latitude. In this series of 500 necropsies no attempts were made to concentrate on rheumatic persons for the reason that in most instances a clinical diagnosis of rheumatic heart had not been made during life. Almost all patients with rheumatic cardiac disease in institutions for persons with mental illness are able to carry on ordinary activity without discomfort. Hence the presence of rheumatic infection remains unrecognized.

If the incidence of rheumatic valvular changes were compiled separately for the various types of psychoses, wide and significant differences would result. In a group of 171 patients with dementia

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1 Goodman, N. G. Benjamin Rush, Physician and Citizen, 1746-1813, Philadelphia, University of Pennsylvania Press, 1934, p. 260. Haskell, R. H. Mental Disturbances Associated with Acute Articular Rheumatism, *Am J Insanity* **71** 361 (Oct) 1914. Winkelman, N. W., and Eckel, J. L. The Brain in Acute Rheumatic Fever. Nonsuppurative Meningo-Encephalitis Rheumatica, *Arch Neurol & Psychiat* **28** 844 (Oct) 1932.

2 Winkelman, N. W., and Eckel, J. L. Endarteritis of the Small Cortical Vessels in Severe Infections and Toxemias, *Arch Neurol & Psychiat* **21** 863 (April) 1929.

3 Bruetsch, W. L. The Histopathology of the Psychoses with Subacute Bacterial and Chronic Verrucose Rheumatic Endocarditis, *Am J Psychiat* **95** 335 (Sept) 1938. Bruetsch, W. L., and Bahr, M. A. Chronic Rheumatic Brain Disease as a Factor in the Causation of Mental Illness, *J Indiana M A* **32** 445 (Sept) 1939. Bruetsch, W. L. Chronic Rheumatic Brain Disease as a Possible Factor in the Causation of Some Cases of Dementia Praecox, *Am J Psychiat* **97** 276 (Sept) 1940. Rheumatic Endarteritis of Cerebral Vessels. Sequel of Rheumatic Fever, *Tr Am Neurol A* **68** 17, 1942.

paralytica, on whom necropsies were done, rheumatic valvular disease was present in only 17 per cent, while in 100 patients with schizophrenia the incidence was 9 per cent. Most of the schizophrenic patients had been inmates for many years, but they were not known to have suffered from active rheumatic fever during their stay in the institution.

The frequency of rheumatic infection among newly admitted patients with mental disease has also been the subject of a survey. Of 549 female patients admitted during the two year period of 1940 and 1941, 6.6 per cent had rheumatic heart disease. An additional 1.5 per cent had a definite history of rheumatic fever or of chorea, but no clinical signs of cardiac involvement. The total incidence of rheumatic infection in the female group was therefore 8.1 per cent.

During the same period 502 male patients were admitted. Of these only 1.6 per cent had a rheumatic heart. One per cent had a history of rheumatic fever or of chorea without cardiac symptoms. Thus a total of 2.6 per cent of male patients had rheumatic infection. The ratio between rheumatic men and women on this basis was approximately 1:3.

When these figures were compared with those for the general population, the difference assumed statistical significance. According to Hedley<sup>4</sup> the incidence of rheumatic heart disease in the United States is conservatively set at about 800,000 to 1,000,000 cases, or less than 1 per cent. The high prevalence of rheumatic cardiac disease among patients with mental disease in itself is highly suggestive that there might be a direct relationship between rheumatic fever and the mental symptoms. However, even before the rate of rheumatic heart disease among such patients had been established, postmortem observations had revealed the interesting fact that long-continued rheumatic infection involved not only the heart but the brain<sup>5</sup> and at times other organs, such as lungs,<sup>6</sup> kidneys<sup>6</sup> and spleen.

#### NATURE OF LATE CEREBRAL SEQUELAE OF RHEUMATIC FEVER

The involvement of the brain consisted most frequently of a recurrent rheumatic obliterating endarteritis, particularly of the small meningeal and cortical vessels, with subsequent gross or microscopic softenings in the cerebral cortex. This condition has been termed "rheumatic brain

disease." A few patients had rheumatic meningoencephalitis. A third type of involvement was cerebral embolism occurring in patients with mitral stenosis during auricular fibrillation.

Rheumatic vascular lesions as a sequel of rheumatic fever were first described as occurring in the myocardium, by Krehl.<sup>7</sup> Later, Von Glahn and Pappenheimer,<sup>8</sup> Karsner and Bayless,<sup>9</sup> and Gross<sup>10</sup> demonstrated rheumatic endarteritis in the vessels of various internal organs. Von Sántha<sup>11</sup> observed similar changes in the cerebral vessels of a young patient with rheumatic chorea.

#### RHEUMATIC BRAIN DISEASE

The term rheumatic brain disease has been borrowed from internal medicine, which speaks of rheumatic heart disease in denoting both valvular and myocardial changes. In the same sense, the designation rheumatic brain disease comprises both the primary changes in the cerebral vessels and the manifold secondary lesions in the gray matter brought about by the proliferative endarteritis of the small meningeal and cortical vessels. There are also clinical similarities. Many persons with rheumatic heart disease are well and unaware of the cardiac condition until an incidental physical examination reveals a heart murmur. Similarly, most patients with mental disease who have rheumatic brain disease appear physically and neurologically well, a heart murmur and a history of previous rheumatic fever giving the only clue to the etiologic background of the mental illness.

The sequence of events in a few clinically and anatomically well observed cases will be given.

At the age of 6 years the patient had chorea. The first mental symptoms appeared at 18, when she became seclusive and expressed delusions of persecution. On her admission to the state hospital, physical examination revealed nothing significant except a mitral murmur, which was not properly interpreted. The diagnosis was dementia precox. At 54 years of age she died of rheumatic mitral stenosis. Histologic examination of the brain revealed meningeal vessels with signs of old and recent obliterating endarteritis, associated with microscopic areas of incomplete softenings in the cortex. In the kidneys old infarctions were present.

7 Krehl, L. Beitrag zur Pathologie der Herzklappenfehler, *Deutsches Arch f klin Med* **46**:454, 1890.

8 Von Glahn, W. C., and Pappenheimer, A. M. Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am J Path* **2**: 235 (May) 1926.

9 Karsner, H. T., and Bayless, F. Coronary Arteries in Rheumatic Fever, *Am Heart J* **9**: 557 (June) 1934.

10 Gross, L., Kugel, M. A., and Epstein, E. Z. Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, *Am J Path* **11**: 253 (March) 1935.

11 von Sántha, K. Ueber Gefassveränderungen im Zentralnervensystem bei Chorea rheumatica, *Virchows Arch f path Anat* **287**: 405, 1932.

4 Hedley, O. F. Rheumatic Heart Disease. A National Health Problem, *Proc A Life Insur M Dir America* (1938) **25**: 163, 1939.

5 Brenner, O. Pathology of the Vessels of the Pulmonary Circulation. Rheumatism of the Pulmonary Arteries, *Arch Int Med* **56**: 1190 (Dec) 1935.

6 Fahr, T. Kurze Beiträge zur Frage der Nephrosklerose. *Deutsches Arch f klin Med* **134**: 366, 1920.

In other words, rheumatic lesions of many years' duration were observed side by side with more recent changes. This suggests that rheumatic fever in a chronic form had been present since the age of 6 years, when the patient had chorea, and that the infection had continued to be mildly active until her death, at 54.

In another patient, aged 39, described as having a well adjusted personality, there developed a schizophrenic psychosis with many ideas of persecution. There was no history of rheumatic fever or of chorea, but her mother had suffered from rheumatism. The heart was of normal size. Cardiac murmurs were not heard or, if audible, were missed by the examiner. Five months after the onset of the psychosis the patient committed suicide by hanging. The brain was grossly normal. However, throughout the cortex of the entire brain microscopic areas of softenings were observed, which at times had progressed into minute cysts extending over several cell layers. The changes in the gray matter were dependent on diseased cortical vessels. On the mitral valve was recurrent rheumatic endocarditis. In the kidneys, spleen, liver and pancreas a few rheumatic endarteritic vessels were noted.

Since rheumatic brain disease in itself is not a fatal condition, most of the patients live out their span of life in an institution for persons mentally ill unless they die prematurely of mitral stenosis or some intercurrent disease or as a result of an accident. It may be argued that the changes in the brain are not related to the mental symptoms and are a later development in the patient's life. In this instance, however, the unusual opportunity had presented itself to study the early manifestations of rheumatic involvement of the brain, which were coincident with the onset of the psychosis.

In these 2 patients the cerebral process had produced the clinical picture of schizophrenia. Modern psychiatry has viewed schizophrenia as a mere maladjustment of the person to the environment. Singer,<sup>12</sup> however, expressed the belief that in some cases a disease process had occurred, and he classified such cases as instances of "schizophrenia, organic type." In those cases in which the illness was obviously a reaction to the environment, the condition was termed "schizophrenia, psychogenic type."

The mental picture of the patients with rheumatic brain disease does not show any characteristic psychopathologic content. The form of the psychosis is determined by the personality and also by the age at which the involvement of the brain occurs.

In 2 instances rheumatic fever had produced cerebral damage in childhood resulting in mental deficiency. When the patients, who also showed

later psychotic manifestations, died at the ages of 43 and 46 respectively of mitral stenosis, obliterating vascular disease of varied age was present. In 1 patient this had produced gross cortical infarctions in the left frontal lobe.

Milder types of mental abnormalities in children following Sydenham's chorea have long been known. At the Emma Pendleton Bradley Home,<sup>13</sup> a hospital which limits its activities to children with emotional disturbances, the number of behavior disorders following rheumatic chorea is next in frequency to postencephalitic personality change.

If the rheumatic involvement of the brain occurs later in life, a psychiatric symptom complex characteristic of that period will be produced.

A woman who had had rheumatic fever at 21 showed mental symptoms resembling involutional melancholia at the age of 51. Seven years previously she had had a slight stroke which left no obvious residue. On her admission to the hospital there was chronic rheumatoid arthritis of both hands and knees. A systolic blow in the mitral and aortic area was heard. The blood pressure was 145 systolic and 80 diastolic. The patient died at the age of 60 of tuberculous spondylitis. In the brain were infarcted convolutions in addition to numerous minute areas of incomplete cortical softenings. There was no arteriosclerosis, and the cerebral process was interpreted as rheumatic. Under the microscope the mitral and aortic valves revealed old and recent rheumatic alterations.

Prior to death this patient was considered as suffering from involutional melancholia on a psychologic basis. Since rheumatic heart disease and mental illness affect an appreciable proportion of the population, psychoses will develop in persons with rheumatic cardiac disease in whom the rheumatic infection does not produce changes in the brain and is unrelated to the mental symptoms. Unfortunately, the clinical picture gives no clue as to whether one is dealing with an organic psychosis or with a mental disturbance on a psychogenic background.

The question has been raised whether a biopsy on the brain would be of value. The rheumatic changes in the brain are evident in some areas and are absent in others. It is characteristic of rheumatic endarteritis that not all vessels are included in the obliterating process and that only short segments are diseased. Postmortem experience has shown that rheumatic lesions are present in only about one half of the brain blocks examined. While a biopsy disclosing rheumatic changes would be proof of the existence of cerebral involvement, a negative result would not exclude the presence of rheumatic brain disease.

12 Sherman, I. C., and Broder, S. B. Dr. H. Douglas Singer's Concept of the Psychoses, *Arch Neurol & Psychiat* 49:732 (May) 1943.

13 Achievements of the First Ten Years, 1931-1941, Emma Pendleton Bradley Home, East Providence, R. I., 1941, p. 11.

Necropsy experience, however, points to the fact that in mentally ill patients with rheumatic heart disease coexisting lesions of the brain are frequent. In only 1 of 30 patients who had rheumatic valvulitis was the brain free of changes. In 15 patients there were gross cortical infarctions, and in the remaining 14 the cerebral changes consisted of microscopic areas of complete and partial softenings in the cortex. With a few exceptions the basal ganglions and other structures of the brain were normal.

Most of this work had been done before electroencephalography had become practical. It will be left for the future to establish possible correlations between electroencephalographic abnormalities and rheumatic cortical lesions.

#### RHEUMATIC ENCEPHALITIS

Meningoencephalitis in patients with rheumatic cardiovalvular disease is of infrequent occurrence. Only 2 instances were observed over a ten year period.

One of these patients was a 47 year old woman, who six weeks prior to admission suddenly became disturbed and required restraint. She talked continually and incoherently, refusing food and water. On admission to the hospital, two days before her death, the patient was delirious and had a temperature of 104 F. The heart sounds were distant. There were no murmurs. The joints were normal. The husband related later that his wife had suffered in previous years from articular rheumatism. Autopsy revealed on an otherwise normal mitral valve a single firm verrucous wart. In the spleen and the kidneys were old and new infarctions. The brain was swollen, and there was fresh softening of the left temporal lobe, due to massive round cell accumulations. Throughout the white matter of the entire brain, including the midbrain and pons, but less in the cortex, were perivascular infiltrations. In the pia-arachnoid were a few localized areas with lymphocytes and plasma cells. Cerebral arteriosclerosis and gross and microscopic signs of syphilis of the aorta and other organs were absent.

#### RHEUMATIC CEREBRAL EMBOLISM

At the beginning of this study it was assumed that the cortical damage which has been termed rheumatic brain disease was caused by minute emboli detaching themselves from the cardiac valves. This thought proved erroneous, and the source of the vascular occlusions was found to have its origin in local proliferation of the intima. Furthermore in studying histologically rheumatic cardiac valves it could easily be seen that embolic material will not detach itself readily from fibrous verrucae.

Rheumatic cerebral embolism develops most frequently in cases of mitral stenosis during auricular fibrillation, the soft newly formed mural thrombi furnishing the material for emboli. The following case will illustrate this type of cerebral involvement.

In a 62 year old woman with a history of repeated attacks of auricular fibrillation in the past year there developed a progressing mental deterioration giving the impression of senile psychosis. At the age of 12 she had had rheumatic fever. There was a mild recurrence of articular symptoms when she was 52. She died of mitral stenosis ten days after admission to the institution. In the brain was a large infarction involving the left occipital-parietal region and extending into the upper temporal convolutions. The cerebral vessels were free of atherosclerotic plaques. No signs of intimal proliferation were observed in these vessels, and the large infarction was interpreted to be the result of an embolic manifestation during one of the attacks of auricular fibrillation in the year preceding the patient's death.

#### RHEUMATIC OBLITERATING ENDARTERITIS IN OTHER NEUROLOGIC CONDITIONS

Rheumatic disease of the vessels of the central nervous system may prove the cause of a number of obscure neurologic conditions in patients with rheumatic heart disease.

A paralytic stroke occurring in middle life has usually been associated with syphilis, even in the absence of positive serologic reactions. If in a young person an unexplained hemiplegia develops and physical examination reveals a mitral or aortic murmur, the correct interpretation of the neurologic symptoms may be on the basis of rheumatic vascular occlusion of one of the larger vessels supplying the internal capsule.

Epileptic seizures appearing in the years following an attack of rheumatic fever or chorea have definitely been traced to rheumatic obliteration of cerebral vessels.<sup>14</sup> Foster<sup>15</sup> has shown that the incidence of convulsive seizures in patients with rheumatic heart disease is from two and a half to seven times higher than in the average population.

A diagnostic problem belonging under this heading has recently been reported.<sup>16</sup> A patient aged 45 was hospitalized with symptoms of epidemic encephalitis. A murmur over the mitral and aortic area with generalized cardiac enlargement was noted, but this observation was not utilized in the interpretation of the clinical picture. Necropsy revealed multiple areas of fresh endarteritic or embolic softenings in the midbrain, which were responsible for the symptoms suggesting epidemic encephalitis. There was aortic stenosis, and on the mitral valve were extensive rheumatic vegetations.

14 Bruetsch, W. L. Rheumatic Epilepsy. Sequel of Rheumatic Fever, *Am J Psychiat* 98:727 (March) 1942.

15 Foster, D. B. Association Between Convulsive Seizures and Rheumatic Heart Disease, *Arch Neurol & Psychiat* 47:254 (Feb) 1942.

16 Alexander, L. The Diseases of the Basal Ganglia, *A Research Nerv & Ment Dis, Proc* (1940) 21:454, 1942.

If encephalitic symptoms appear in a person with rheumatic heart disease, the thought should always be kept in mind that the patient may be suffering from rheumatic cerebral involvement of an encephalitic, endarteritic or embolic type. This is true especially if there is no epidemic and other types of encephalitis can be excluded.

#### CONTINUITY OF RHEUMATIC FEVER

The study has brought out the continuity of rheumatic fever in a chronic form throughout the entire lifetime of the patient and in the absence of any symptoms which are generally regarded as evidence of activity. In many instances mild activity could be demonstrated in the tissue of the mitral or aortic valve, consisting of loosely arranged foci of round cells, of occasional fibroblasts in the stage of cell division or of minute collections of fibrin along the closing border which were undergoing organization. Likewise, in the brain and in other organs vascular changes of varied age could be observed, which revealed that the rheumatic process was recurrent and was still slightly active, although the original attack of rheumatic fever had taken place sometimes several decades before. It is evident, then, that the term "inactive rheumatic fever," which of late has been used for rheumatic conditions, without obvious clinical symptoms, should be employed with caution.

#### SUMMARY

A late sequel of rheumatic fever is obliterating endarteritis, which usually develops while the patient is otherwise in good health. If the vascular process involves the small meningeal and cortical vessels, gross and microscopic infarctions in the gray matter of the brain will result, producing a variety of mental symptoms. This type of cerebral involvement has been termed "rheumatic brain disease." It represents a chronic infectious process in the same sense as rheumatic heart disease.

Although widespread and clinically manifest obliterating arteritis seems to occur in only a small number of patients with rheumatic heart disease, the possibility of the development of rheumatic endarteritis in such persons appears to be ever present.

Rheumatic fever in the form of this late cerebral sequel has been found to be an important factor in the causation of mental illness. The fact that rheumatic heart disease is several times more frequent among mentally ill patients than in persons of the general population emphasizes this contention.

Other late cerebral sequelae of rheumatic fever are rheumatic encephalitis and cerebral embolism, the latter occurring most often during auricular fibrillation in patients with mitral stenosis.



# Progress in Internal Medicine

## DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1943

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WITH THE EDITORIAL ASSISTANCE OF PAUL D WHITE, M D  
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Despite the war, special interest has continued and work has been done in certain fields of cardiovascular disease, particularly in electrocardiography, congenital defects, arrhythmias and hypertension. There are many problems relating to cardiovascular disease in wartime, which are of significance but which have not been published because of censorship or other restrictions. For this reason, this paper is mostly concerned with the advances made in civilian practice.

### ANATOMY, PHYSIOLOGY AND METHODS

Observations on velocity of blood flow have been used for a long time to assist in the diagnosis of heart failure, to help judge the severity of the failure and to evaluate the results of therapy. Unfortunately many of the methods in current use require intelligent cooperation on the part of the patient to produce a good end point.

Esser and Berliner<sup>1</sup> devised a test to show variations in circulation time in the individual patient, using saccharin. Sixty patients were used in the experiment, and the circulation time was first measured. After one hour the determination was repeated, with the same dose of the same drug. In only 6 cases were the results identical. In the remaining 54 the figures disagreed by values from 1 per cent to 143 per cent of the original. At first glance it might be thought that this could be accounted for by assuming that the patient was better prepared to judge the end point in the second experiment by virtue of his experience with the first. However, the time in the second test was prolonged as often as it was shortened in comparison with the first. About half the patients were tested under basal conditions, and in this group the results were somewhat better than in the total number, suggesting that the period of adjustment to rest between the two tests might have had something to do with the variable result. The authors concluded that the saccharine test for

circulation time should be performed under basal conditions and that it should not be relied on to test the progress or course of the patient with cardiac disease.

Koster and Sarnoff<sup>2</sup> used theophylline ethylenediamine in a dose of 1 cc of solution (0.24 Gm) intravenously to measure the circulation time, taking as an end point the involuntary respiratory gasp. They reported a sharp end point, with only 1 failure in 72 cases. This is an objective method which does not depend on the variable subjective reactions of the patient.

Lange and Boyd<sup>3</sup> stress the need for a purely objective measurement of circulation time. They recommend an improvement on a technic previously reported by the first author, using fluorescein intravenously. A light source of mercury vapor with a purple glass filter is directed against the lips of the patient, which acquire a greenish yellow hue when the substance reaches the capillaries in the lips. The end points they obtained were very sharp, and repeat determinations of circulation time showed excellent results, the values never differing more than three seconds. In the majority of cases the difference was two seconds or less. They included observations on normal persons and on patients with heart disease, bronchial asthma and hyperthyroidism.

Gross<sup>4</sup> has extended the usual measurements of vital capacity to include other functions of respiration which are said to have more diagnostic significance than the vital capacity alone. He timed the minimum duration of the expiration which represented vital capacity and then calculated the velocity of expiration by dividing the vital capacity by the minimum duration of expiration. A third function, expiratory pres-

From the Cardiac Laboratory of the Massachusetts General Hospital.

1 Esser, K. H., and Berliner K. Duplicate Measurements of Circulation Time Made with the Saccharine Method, *Ann Int Med* 19 64, 1943.

2 Koster, H., and Sarnoff, S. J. Circulation Time. A Review of Previous Methods and the Introduction of Aminophyllin as a New Agent, *J Lab & Clin Med* 28:812, 1943.

3 Lange, K., and Boyd, L. J. Objective Methods to Determine the Speed of Blood Flow and Their Results (Fluorescein and Acetylene), *Am J M Sc* 206 438, 1943.

4 Gross, D. Investigations Concerning Vital Capacity, *Am Heart J* 25 335, 1943.

sure, was measured by having the patient breathe into a tube connected with a mercury blood pressure manometer. These quantities were then determined on 30 normal persons of the same age, 10 patients with congestive heart failure and 10 patients with pulmonary disease, including emphysema and asthma. He also studied a miscellaneous group of 10 patients having either pulmonary or cardiac disease but not both. There was no relation between the vital capacity and the expiratory pressure. In those subjects who showed decrease in vital capacity due predominantly to cardiac disease the expiratory time was prolonged, the velocity of the spirometric expiration was decreased and, most significant, the expiratory pressure was decreased greatly, typically falling below half of the standard value.

Measurements on patients with pulmonary disease, on the other hand, showed considerable prolongation of the expiratory time, a distinct decrease in velocity of expiration and no significant change in expiratory pressure. One group of patients with normal vital capacity showed abnormal expiratory pressure or expiratory velocity. All of these had cardiac or pulmonary disease. For these patients the new measurements were helpful in uncovering apparent abnormalities not evident in the measurement of vital capacity. These methods may be of some value in studying the physiologic basis of disturbances of respiration in cardiac and pulmonary disease.

Warren and Stead<sup>5</sup> studied the effect of the accumulation of blood in the extremities on venous pressure in 6 normal subjects. They applied venous tourniquets at a pressure of 85 mm of mercury to the thighs, producing an average fall of venous pressure in the external jugular vein of 53 mm of water and in the antecubital vein of 23 mm. They explain this difference by pointing out that veins of the arms tend to collapse when venous pressure is lowered and that further lowering of pressure proximal to the collapse produces no further decrease in venous pressure in the distal part of the vein. In advanced cardiac failure, when the venous bed is already distended by greatly increased venous pressure, the veins cannot be distended much farther and therefore the value of application of tourniquets may be small. Also, in the presence of marked edema of the extremities the high tissue pressure may prevent the accumulation of large amounts of blood in the veins.

5 Warren, J. V., and Stead, E. A., Jr. Effect of the Accumulation of Blood in the Extremities on Venous Pressure in Normal Subjects, *Am J M Sc* **205** 501, 1943.

May<sup>6</sup> describes a new and simple clinical method of measuring venous pressure in the patient with cardiac disease. With the subject in the upright position, the veins of the under surface of the tongue are observed. Since the veins in the tongue lie about 200 mm above the right auricle in the average patient, they will be collapsed with the subject erect unless the venous pressure is abnormally high, that is, greater than 200 mm, in which case distention or venous pulsation has been noted.

Bartlett and Carter<sup>7</sup> advocate the routine use of electrocardiography and phonocardiography as a screening process in the detection of cardiovascular disease. They suggest that such methods might be valuable as applied to large numbers of persons in much the same way that the tuberculin test and roentgen examination are used to separate tuberculous from noninfected persons. They imply that the advantages to be gained lie in the ability to examine large numbers with routine methods which can be carried out by technicians. They also imply that such methods will often reveal abnormalities not evident to a skilled observer on physical examination.

The present day emphasis on primary value of mechanical aid, in auscultation especially, is unfortunate. Not only does it overlook the fact that the detection of murmurs by phonocardiography often requires the proper placing and selection of microphones, but it gives a false sense of security in relying on these aids. Certainly the value of electrocardiography as a screening process, especially for young persons, is slight, and it is well known that considerable persistence may be required to record by mechanical methods auscultatory abnormalities obvious to trained ears.

#### ARRHYTHMIAS

In the past the occurrence of auriculoventricular block in the presence of auricular paroxysmal tachycardia has been considered a rather rare event. In a comprehensive article Barker, Wilson, Johnston, and Wishart<sup>8</sup> review 17 previously reported cases of this phenomenon and add 8 new cases. They state that the abnormality may occur at any age in persons with organic

6 May, A. M. The Tongue Sign for High Venous Pressure, *Am Heart J* **26** 495, 1943.

7 Bartlett, W. M., and Carter, J. B. Combined Electrocardiography, Stethography and Cardioscopy in the Early Diagnosis of Heart Disease, *Ann Int Med* **19** 271, 1943.

8 Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W. Auricular Paroxysmal Tachycardia with Auriculoventricular Block, *Am Heart J* **25** 765 1943.

heart disease or with otherwise normal hearts. In 60 per cent of their cases the P waves were upright, which suggested an origin near the sinoauricular node. They believe that auriculoventricular block is more likely to develop when the arrhythmia originates near the sinoauricular node than when its origin is near the auriculoventricular node. This auricular paroxysmal tachycardia with auricular block is considered somewhat different from the common types of auricular paroxysmal tachycardia and bears some resemblance to auricular flutter in the following characteristics: partial auriculoventricular block, long duration, slowing of the auricular rate with quinidine, conversion to auricular fibrillation in a few cases with large amounts of digitalis, increase in the degree of auriculoventricular block with pressure on the carotid sinus but rare conversion to normal rhythm, and lack of response to mecholyl. It differs from flutter in that the auricular deflections are always separated by an isoelectric interval in the electrocardiogram, which never occurs in flutter, although esophageal leads may sometimes be necessary to demonstrate the continuous oscillation of the circus wave in flutter. They believe that most of the features of this type of paroxysmal tachycardia can be accounted for by a circus rhythm involving either the sinoauricular or the auriculoventricular node.

In another article, which represents an extension and elaboration of these ideas, Barker, Johnston and Wilson<sup>9</sup> report a study of the electrocardiograms of 100 patients with auricular paroxysmal tachycardia. Ten patients had a slight irregularity characterized by alternation in the lengths of the cycles. The contours of the auricular deflections were uniform, and the authors believe this requires that "the longer and shorter paths be close together throughout their courses, or at least in that part which lies in auricular muscle, which makes a major contribution to P deflection." The variation observed was often considerable, frequently 0.05 second and often as great as 0.1 second. They suggest that alternation of cycle length may be accounted for if it is supposed that paroxysmal auricular tachycardia is caused by a circus rhythm involving the sinoauricular or the auriculoventricular node. "There is evidence that tissues of both these nodes have a relatively long refractory period, and that conduction in the latter, at least, is relatively slow. Thus a relatively slight alternation in the length of the path through one of the nodes could cause a considerable change in dura-

tion of the cycle without modifying the form of auricular deflection."

Barker, Wilson and Johnston<sup>10</sup> in still another article on the mechanism of auricular paroxysmal tachycardia present a summary of their own ideas and those of others pertaining to the physiologic characteristics of this mechanism. They believe that the underlying mechanism of auricular paroxysmal tachycardia is a circus rhythm in the auricles, the path of which passes through one of the specialized auricular nodes. In support of this belief they list the following facts. There is evidence to show that the action of events outside the heart on the arrhythmia is concentrated on the specialized auricular nodes. Slowing of the auricular rate and termination of paroxysms are produced by vagal stimulation and by digitalis, and acceleration of the rate, by exercise. As previously stated, auriculoventricular block in paroxysmal tachycardia is rare in cases in which there are inverted auricular deflections.

Further support for the theory of circus rhythm is found in the abrupt nature of the onset and termination of attacks, the remarkable stability of the rate, slowing of the auricular rate and termination of the attacks by quinidine. The occasional alternation in cycle length, as mentioned in the previous article, is another point in support of the theory. They mention several exceptions which cannot be explained by circus rhythm. In rare cases the rate slows gradually to normal instead of terminating abruptly. It is considered that these probably are not examples of true auricular paroxysmal tachycardia but rather represent an unusual and persistent type of sinus tachycardia. Also, auricular deflections of varying form are sometimes seen in auricular tachycardia, which suggests different origin of impulses in different regions of the auricles.

Another rare type of this disorder is that which shows an inverted P wave in lead I and an upright P wave in leads II and III. It is believed that the form of the deflections suggests an origin in the upper part of the left atrium far from the nodes of specialized tissue. But such cases are decidedly uncommon. Only 2 were encountered among 100 unselected cases studied.

Decherd, Herrmann and Schwab<sup>11</sup> collected 40 cases of paroxysmal auricular tachycardia in which there was auriculoventricular block. Only cases in which dropped ventricular premature

9 Barker, P. S., Johnston, F. D., and Wilson, F. N. Auricular Paroxysmal Tachycardia with Alternation of Cycle Length, *Am Heart J* 25:799, 1943.

10 Barker, P. S., Wilson, F. N. and Johnston, F. D. The Mechanism of Auricular Paroxysmal Tachycardia, *Am Heart J* 26:435, 1943.

11 Decherd, G. M., Herrmann, G. R. and Schwab, E. H. Paroxysmal Supraventricular Tachycardia with A-V Block, *Am Heart J* 26:446, 1943.

beats appeared were included. A prolonged P-R interval alone was not considered of sufficient importance to warrant inclusion of the case in the series. The cases were selected from 102 instances of supraventricular paroxysmal tachycardia of varying duration, an incidence of about one third. The authors explain this high incidence by stating the fact that most of the records were obtained from patients who had been hospitalized for cardiac disease. Only 2 had normal hearts, and, in addition, most patients had received digitalis and quinidine. The form of the deflection of the P wave, which would have been of some interest in the light of the data presented in the articles just preceding, is not described specifically.

Cooke and White<sup>12</sup> prepared a study of ventricular paroxysmal tachycardia comprising 27 cases. This article was summarized in detail in last year's review on "Diseases of the Heart" published in this journal.<sup>13</sup>

Williams and Ellis<sup>14</sup> report 36 cases of the same abnormality collected from a series of 60,000 electrocardiograms. In all but 1 case organic heart disease was present. Toxicity due to digitalis was found to be the most frequent precipitating factor, with myocardial infarction next. It is emphasized again that the prognosis in such cases is that of the underlying heart disease. The use of chest leads as a valuable aid in the diagnosis of ventricular tachycardia is described. The chest electrode was placed in the third right interspace at the sternal border, and in several instances P waves which could not be seen in the standard leads were demonstrated. Since the diagnosis often depends on establishing the presence of an independent auricular rhythm, this procedure is considered to be of some value, except in cases of coexisting auricular fibrillation or auricular standstill.

Edeiken<sup>15</sup> adds 2 cases of extreme tachycardia with a ventricular rate of 300 or more to the 15 cases already reported in the literature. Probably in only 1 of these cases was the abnormality of ventricular origin. It was thought that treatment probably had little effect on the arrhythmias. Three of the infant patients died during a paroxysm.

12 Cooke, W. T., and White, P. D. Paroxysmal Ventricular Tachycardia, *Brit Heart J* 5 33, 1943.

13 Graybiel, A., and White, P. D. Diseases of the Heart. A Review of Significant Contributions Made During 1942, *Arch Int Med* 71 713 (May) 1943.

14 Williams, C., and Ellis, L. B. Ventricular Tachycardia, *Arch Int Med* 71 137 (Feb) 1943.

15 Edeiken, J. Extreme Tachycardia with Report of Non-Fatal Paroxysms Following Myocardial Infarction, *Am J M Sc* 205 52, 1943.

# TREATMENT OF ARRHYTHMIAS

Sampson, Alberton and Kondo<sup>16</sup> present a good review of the present knowledge of the relation of administration of digitalis to potassium balance in the heart and add some observations of their own. In experiments carried out on a number of patients they showed that ectopic beats caused by digitalis could be abolished in every instance by oral administration of a potassium salt (potassium acetate in a dose of 5 to 10 Gm). They also studied the fasting potassium level of the blood serum and showed that there was no relation between that quantity and the presence or absence of ectopic ventricular beats. Furthermore, in a study of the curves of rise and fall of serum potassium in relation to the oral administration of potassium acetate, no significant differences occurred during administration of digitalis, even with toxic doses. Also, in many instances the serum potassium remained at fasting levels for a long period before ectopic beats again appeared. They suggested that lack of quantitative relationship between the serum potassium level and the occurrence of ectopic beats suggested fixation of potassium to cardiac muscle or alteration of the state of that muscle by potassium. It was believed that these findings offered positive evidence that the disturbance of potassium balance in the heart muscle is related to administration of digitalis.

Boyd and Scherf<sup>17</sup> employed intravenous injections of magnesium sulfate in the treatment of 11 patients with paroxysmal arrhythmia, who included 2 patients with ventricular tachycardia, 8 with auricular tachycardia and 1 with auricular flutter. Injection of a 10 per cent solution of the drug was beneficial in three out of eight attacks, while a 20 per cent solution succeeded in eight out of eight attacks. The auricular flutter was not affected. As possible toxic consequences of the injections the authors cited increase of the PR interval and ventricular extrasystoles appearing for a short time following. No serious reactions were observed. However, the authors hesitate to use the drug in the presence of extreme myocardial damage, serious disturbances in auriculoventricular conduction or gallop rhythm.

Sagall, Horn and Riseman<sup>18</sup> studied the effects of oral and intramuscular administration of

16 Sampson, J. J., Alberton, E. C., and Kondo, B. The Effect on Man of Potassium Administration in Relation to Digitalis Glycosides, with Special Reference to Blood Serum Potassium, the Electrocardiogram and Ectopic Beats, *Am Heart J* 26 164, 1943.

17 Boyd, L. J., and Scherf, D. Magnesium Sulfate in Paroxysmal Tachycardia, *Am J M Sc* 206 43, 1943.

18 Sagall, E. L., Horn, C. D., and Riseman, J. E. F. Studies on the Action of Quinidine in Man, *Arch Int Med* 71 460 (April) 1943.

quinidine on 16 persons, 11 of whom were normal. First a control electrocardiogram was taken, then more tracings were taken at fifteen minute intervals for one hour, with subsequent tracings during the ensuing eight to fifteen hours at less frequent intervals. At the end of twenty-four hours a final record was taken. A number of methods of giving the drug were used. In every case the effect of the drug was evidenced by a prolongation of the QT interval, which was much more constant than the effect on the T wave. Shortly after the administration of a single dose of quinidine or quinine by mouth, the prolongation of the QT interval became maximum in one-half hour to three hours, was maintained in slightly lesser degree for three to five hours and was no longer evident at the end of twenty-four hours. From these studies they concluded that quinine was much less effective than quinidine and that larger doses of the latter caused production of a more prolonged effect and were evident sooner but did not alter the time of maximum response. The response to quinidine given by the intramuscular route was much more prompt and the magnitude of effect was slightly greater but the duration varied little from that observed with the oral method. They concluded that in the treatment of acute arrhythmias a dose should be given every two to two and a half hours.

In another article, Sturnick, Riseman and Sagall<sup>19</sup> report on the clinical use of a soluble quinidine preparation suitable for intramuscular injection. The mixture contains 0.15 Gm per cubic centimeter of quinidine, with a similar amount of antipyrine and 0.2 Gm of urea. The latter two drugs increase the solubility of the quinidine but have no other effect. The authors state that a search of the literature revealed no preparation of quinidine in sufficient concentration to warrant intramuscular use, the formula just given was obtained from the Cinchona Institute.

Their clinical observations were carried out on persons with a representative group of cardiac arrhythmias, including both auricular and ventricular tachycardias. From the results of their work the following dosage is recommended. An initial amount of 0.45 to 0.60 Gm intramuscularly is considered the minimal effective dose. Response to each dose should be observed for one and a half to two and a half hours. If con-

version to normal rhythm does not occur, the initial dose, or a slightly larger one, should be administered. This preparation is particularly valuable when absorption from the gastrointestinal tract is delayed or unreliable (in the presence of vomiting or shock) and when rapid therapeutic action is desired.

This type of quinidine preparation has been used at the Massachusetts General Hospital since its introduction by Riseman. Besides its use in the situations already mentioned, it has proved of value for seriously ill patients in whom arrhythmias developed after thyroidectomy.

Geffer and Leaman<sup>20</sup> gave 0.5 mg of ouabain to 33 patients with rapid cardiac arrhythmias of auricular origin. They concluded that it is an effective agent for treating these disorders. No serious toxic effects were encountered, and the incidence of vomiting was low. Like digitalis, the drug was ineffective against simple tachycardias or in the presence of severe complicating infection.

#### ELECTROCARDIOGRAPHY

In the past few years a schism has arisen among students of electrocardiography, separating them into two well defined schools of thought. The argument centers about the question of validity of Einthoven's equilateral triangle hypothesis. Although the routine work in clinical electrocardiography has not been greatly influenced as yet by the divergence of opinion, the latter may be of importance in determining new directions of investigation. It has already stimulated much lively discussion.

In 1941 Wolferth, Livezey and Wood<sup>21</sup> published the first of their series of articles attacking the Einthoven triangle hypothesis, particularly the assumptions that the body acts as a homogeneous fluid conductor and that the heart functions as an electrical point with regard to each of the three extremities.

In 1942<sup>22</sup> they reported further observations relating to distribution of potential over the surface of the body. They found that variations in potential along radial lines extending roughly from the heart to the tip of each shoulder did

20 Geffer, W. I., and Leaman, W. G. The Use of Ouabain in Rapid Cardiac Arrhythmias, *Am J M Sc* 205 190, 1943.

21 Wolferth, C. C., Livezey, M. M., and Wood, F. C. The Relationships of Lead I, Chest Leads from the C-3, C-4, and C-5 Positions, and Certain Leads Made from Each Shoulder Region. The Bearing of These Observations upon the Einthoven Equilateral Triangle Hypothesis and upon the Formation of Lead I, *Am Heart J* 21:215, 1941.

22 Wolferth, C. C., Livezey, M. M., and Wood, F. C. Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms, *Am J M Sc* 203 641, 1942.

19 Sturnick, M. I., Riseman, J. E. F., and Sagall, E. L. Studies on the Action of Quinidine in Man. Intramuscular Administration of a Soluble Preparation of Quinidine in the Treatment of Acute Cardiac Arrhythmias, *J A M A* 121 917 (March 20) 1943.



not change significantly except for decrement as the distance from the heart increased. These relationships were different from what Einthoven conceived them to be, in the opinion of the authors.

In 1943 the same authors<sup>23</sup> amplified their observations presented in the previous articles and have added further experimental work bearing particularly on potential change below the diaphragm. Their position is aptly summarized in the following sentence:

If, as our studies seem to indicate, the patterns of potential variation found on limbs are each derived mainly from separate parts of the heart and are subject to modification, depending on electrical and anatomical characteristics of the tissues which form the pathways between the epicardium and the extremities, limb leads do not merit the scientific standing that they have been supposed to possess and there seems to be little reason to continue making them.

The authors believe that there are only three important patterns distributed over the body from the heart as a center, designated as the "C-1" pattern, found on the right side of the chest, the "extra-apical," or "C-5," pattern, found on the left side of the chest, and the "diaphragmatic" pattern, found below the heart and over the abdomen. For routine study they recommend chest leads C-1 to C-6<sup>24</sup> paired with an indifferent electrode placed at the right scapula, which shows, in their estimation, minimal potential variation. The area below the diaphragm has not been well explored as yet and is suggested as a field for further investigation.

It is suggested that elimination of much of the confusion that now exists in clinical electrocardiography could be effected by dispensing with the limb leads.

The other school of thought, represented by Wilson and his co-workers, uses the Einthoven triangle hypothesis as a working basis for its theories of electrocardiography. While those who belong to this school admit that Einthoven's hypothesis may not be entirely valid, they believe that for most purposes of clinical electrocardiography and for theoretic concept the assumptions are adequate.

Those who support this approach to the subject have used vector analysis in an ingenious fashion to explain the variations in potential found in the electrocardiogram, and in their work

the findings in the limb leads are given great importance.

Bayley<sup>25</sup> has written a comprehensive summary of the application of electrocardiographic theory to the interpretation of electrocardiograms. While his approach involves the use of higher mathematics, he has introduced a method of geometric visualization useful to those who are not familiar with advanced mathematics. He states that "the well established laws which define the flow of electric currents in homogeneous volume conductors are applicable to the interpretation of the electrical effects produced by the heart beat with sufficient accuracy to be of great clinical usefulness. The uniformly accurate diagnostic results obtained, particularly in the problem of local myocardial ischemia and infarction, appear to completely justify the adoption by Wilson et al of certain well established physical laws for the interpretation of clinical effects produced by the heart beat."

One of the chief objections held by those who doubt the validity of Einthoven's hypothesis is directed against the assumption that the heart is immersed in a homogeneous electrical medium. The answering argument maintains that this is so for practical purposes, at least, although lung, mediastinal tissue, etc., may not constitute a homogeneous medium in the absolute sense.

Kaufman and Johnston<sup>26</sup> have attempted physical measurements in living tissue in order to answer this question more specifically. The article begins with a technical description of development, properties and use of simple electrode systems employed to measure the specific resistance of living tissue *in situ*. Measurements were made on muscle, normal inflated lung and liver of anesthetized dogs, and it was found that these tissues have specific resistance in the same order of magnitude. Measurement of the resistance of cardiac muscle during diastole was found to be difficult when the heart was beating rapidly but was approximately one third that of lung, muscle and liver tissue and about the same as that of blood.

In the words of the authors, "these measures establish experimentally the validity of the assumption that the errors in theoretical studies of the form of the electrocardiogram made by considering the tissues which surround the heart

23 Wolferth, C. C., Livezey, M. M., and Wood, F. C. Distribution of the Patterns of Ventricular Potential Which Determine the Forms and Significance of Electrocardiograms, *Am J M Sc* 205 469, 1943.

24 Nomenclature and Criteria of Diagnosis of Diseases of the Heart. Criteria Committee of American Heart Association, ed 4, New York, American Heart Association, 1939.

25 Bayley, R. H. On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease, *Am Heart J* 26 769, 1943.

26 Kaufman, W., and Johnston, F. D. The Electrical Conductivity of the Tissues Near the Heart and Its Bearing on the Distribution of the Cardiac Action Currents, *Am Heart J* 26 42, 1943.



uniform with respect to their specific resistivity, are of no practical importance."

In 1934 Wilson, Macleod, Barker and Johnston<sup>27</sup> introduced the concept of ventricular gradient as a new method for analysis of the electrocardiogram. The areas of deflections of the QRS complex were used to determine the mean electrical axis of QRS, and the areas of deflections of the T wave were used to determine the mean electrical axis of T in the same manner that the amplitude of deflection of QRS is ordinarily used to determine the electrical axis of QRS, based on the hypothesis of Einthoven's equilateral triangle. By adding algebraically the area of QRS and the area of T and proceeding in the same fashion it is possible to calculate the direction and magnitude of the manifest area of QRS-T. This quantity is a vector, having both direction and magnitude, to which the name "ventricular gradient" was given by Wilson and his associates. In their opinion the area of QRS-T is a measure of the electrical effects produced by local variations in the excitatory process, while its mean electrical axis gives the direction of the line along which the local variations are greatest.

Ashman, Byer and Bayley<sup>28</sup> offer a clear exposition of the concept of ventricular gradient, using simple examples. They point out that the magnitude and direction of ventricular gradient in conjunction with the QRS vector are an expression of the size and direction of the T wave. A change in the gradient reveals a change in the state of the muscle. Some changes in the T wave however, such as those in bundle branch block, are directly related to change in QRS.

In a companion article<sup>29</sup> they studied several of the factors, including change in heart rate and posture, which affect Wilson's ventricular gradient and manifest magnitudes of the mean QRS axis. The study implies that changes in the T wave can be evaluated properly only when considered in relation to the magnitude and directions of the mean QRS and QRS-T area. The present chaotic state in electrocardiographic criteria is discussed, and the authors

believe that this method of analysis may prove to be a more constant and accurate gage of myocardial change. At the same time, they do not assert that directions of vectors as given necessarily represent their true direction in three-dimensional space. Vector analysis is considered to be of fundamental importance in the solution of electrocardiographic problems.

Further studies of the normal human ventricular gradient were carried out by Ashman, Gardberg and Byer,<sup>30</sup> extending the attempt to set up normal criteria for electrocardiography. Using roentgenograms to define the anatomic axis of the heart, they went on to study the relationship between this entity and the electrical axes (QRS axis and ventricular gradient). A device equipped with a source of light and models of the heart was utilized, the model was projected on a chart. Admittedly much more work must be done before the limits are fixed, but tentative figures have been obtained from this study. The details of these investigations do not lend themselves to a brief review.

Ashman<sup>31</sup> studied the relationship between the magnitudes of the manifest mean areas of the QRS complex, the ventricular gradient and deviations of the RS-T segment. He believes that one type of deviation of the RS-T segment is a normal physiologic phenomenon related to these magnitudes. The second type is related to abatement or reversal in the direction of flow of a current of injury or to intramuscular blocking of a wave of excitation or to a combination of both factors, as in recent myocardial infarction or acute pericarditis.

In the analysis the concept that a diphasic ventricular complex of the electrocardiogram is produced by the summation of two monophasic curves was used with full realization of the limitations of the method. It was shown that the deviations of the RS-T segment observed in human electrocardiograms agreed with the theoretic expectations. It is held that the present terminology for deviation of the RS-T segment is unsatisfactory, because it fails to take into account the two entirely different mechanisms of production of the segment. It is suggested that deviations of the type described in the article be called "repolarization or regression deviations," but those produced by injury or muscle depression and blocking be called "injury

27 Wilson, F. N., Macleod, A. G., Barker, P. S., and Johnston, F. D. The Determination and the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, *Am Heart J* **10** 46, 1934.

28 Ashman, R., Byer, E., and Bayley, R. H. The Normal Human Ventricular Gradient. I. Factors Which Affect Its Direction and Its Relation to Mean QRS Axis, with Appendix on Notation, *Am Heart J* **25** 16, 1943.

29 Ashman, R., and Byer, E. Normal Human Ventricular Gradient. II. Factors Which Affect Its Manifest Area and Its Relationship to Manifest Area of QRS Complex, *Am Heart J* **25-36**, 1943.

30 Ashman, R., Gardberg, M., and Byer, E. The Normal Human Ventricular Gradient. III. The Relation Between the Anatomic and Electrical Axes, *Am Heart J* **26** 473, 1943.

31 Ashman, R. The Normal Human Ventricular Gradient. IV. The Relationship Between the Magnitudes AQRS and G, and Deviations of the RS-T Segment, *Am Heart J* **26** 495, 1943.

deviations," and that characteristic slight deviations due to the presence of a large ventricular gradient be called "gradient deviations"

Gardberg and Ashman<sup>32</sup> present in graphic fashion, illustrated by models, a way in which vector analysis based on Einthoven's triangle, plus a knowledge of the sequence of activation of parts of the heart, can explain the production of the QRS complex

They also present explanations of the variations in the QRS complex which should appear when the heart is rotated to different positions within the thorax. In making the analysis they have correlated findings in the experimental animal, known effects of rotation of the heart in man produced by normal procedures or certain pathologic conditions, known effects of bundle branch block or infarction, and information derived from studies of precordial leads

Viscidi and Geiger<sup>33</sup> criticize the current criteria of normality for the electrocardiogram and report a study of the electrocardiograms of 500 apparently healthy young working adults. One half of the records in the study fell outside the range of normal as defined by the criteria of normality for the American Heart Association.<sup>21</sup> Borderline and abnormal electrocardiograms were then reinvestigated, and only 14 presented either definite or probable abnormalities

Gubner and Ungerleider<sup>34</sup> suggest specific electrocardiographic criteria for the diagnosis of hypertrophy of the left ventricle. This project was undertaken as part of a study of hypertension, and the material comprised three groups. In the first were 460 applicants for insurance whose electrocardiograms showed deviation of the axis to the left and who had blood pressures below 140 systolic and 90 diastolic, with no record or finding of cardiac impairment. In the second group were 380 applicants with hypertension and deviation of the axis to the left, whose blood pressure was above 140 systolic and 90 diastolic. The third group was made up of 100 subjects with advanced hypertensive heart disease and deviation of the axis to the left in whom it may be assumed that left ventricular hypertrophy was present. Five combinations of R and S waves in the standard limb leads were investigated. The combination of  $R_1$  and  $S_3$  was found to be most efficient. Results of the study are sum-

marized. Hypertrophy of the left ventricle may be considered to be present when deviation of the axis to the left occurs in association with any of the following conditions: (1) increase in amplitude of the QRS complex when the sum of R in lead I and S in lead III is over 25 millivolts (hypertrophy is probably present if this sum exceeds 22 and is suggested when it exceeds 20), (2) depression of the ST segment in lead I of any perceptible degree, even as slight as 0.5 mm, (3) flattening of the T wave below 1 mm in amplitude or further degrees of abnormality of the T wave in lead I

Increase in amplitude of QRS as described is considered more specific than changes in the ST segment or in the T wave. The authors suggest that the increase in QRS complexes was due to an increase in muscle mass, while the changes in the ST segment and in the T wave resulted from relative ischemia of the subendocardial muscle. That region is particularly vulnerable because of intramyocardial pressure gradient during contraction

Hurwitz, Langendorf and Katz<sup>35</sup> analyzed the electrocardiograms from 369 cases of myocardial infarction with especial reference to the details of the QRS pattern, in the hope that it might be of use in differential diagnosis of myocardial infarction in the future. The most significant findings were related to the QRS patterns revealed by the limb lead in cases of infarction of the anterior wall. Of special interest was the apparent relative unimportance of the  $Q_1$ ,  $T_1$  pattern, which was present in only 25 per cent of the cases of anterior infarction. In 32 per cent there was a deep  $S_2$ ,  $S_3$  pattern, with over one half of these showing a low  $QRS_1$ . In the other half of the 32 per cent QRS was normal in size. A low  $QRS_1$  was present in 37 per cent of the cases. On the other hand, in 90 per cent of the 141 cases of infarction of the posterior wall there was a  $Q_3$  or a  $Q_2$ ,  $Q_3$  pattern

As far as appraisal of old infarction is concerned, the  $S_2$ ,  $S_3$  pattern must be differentiated from the picture of left ventricular strain produced by hypertension or valvular heart disease. This is not always possible, but the finding of a low  $QRS_1$  makes the differentiation easy. When  $QRS_1$  is of normal size, the chest leads may be helpful

Another pattern of interest is that of the inverted  $QRS_1$  with upright  $QRS_3$ . This may be differentiated from the picture produced by right ventricular strain with the help of T wave and chest lead patterns

32 Gardberg, M., and Ashman, R. The QRS Complex of the Electrocardiogram, *Arch Int Med* 72: 210 (Aug) 1943

33 Viscidi, P. C., and Geiger, A. J. Electrocardiographic Observations on 500 Unselected Young Adults at Work, *Am Heart J* 26: 763, 1943

34 Gubner, R. S., and Ungerleider, H. E. Electrocardiographic Criteria of Left Ventricular Hypertrophy, *Arch Int Med* 72: 196 (Aug) 1943

35 Hurwitz, M. M., Langendorf, R., and Katz, L. N. The Diagnostic QRS Patterns in Myocardial Infarction, *Ann Int Med* 19: 924, 1943

Dressler<sup>36</sup> reports an electrocardiographic pattern of value in the diagnosis of myocardial infarction. The significant changes in anterior wall infarction, such as elevation of the ST segment and inversion of the T wave in lead I, are well known. In some instances of infarction of the anterior wall these signs are poorly developed or occur rather late. Instead of sharp inversion there is sometimes but slight flattening of the T wave, which remains upright or becomes isoelectric. In such cases the reciprocal alterations in lead III are often marked. Evidence from his own observations and from reports in the literature indicates that the electrocardiographic pattern in which  $T_3$  is greater than  $T_1$  is in the great majority of cases equivalent to the anterior type of myocardial infarction. This is especially true in the cases of older persons who have a history of angina pectoris.

Other factors may occasionally cause reversal of the normal relationship of  $T_1$  to  $T_3$  ( $T_1$  greater than  $T_3$ ). A vertical position of the heart in the absence of heart disease, pulmonary emphysema, occasionally rheumatic heart disease, and rarely congenital heart disease, thyrotoxicosis, anemia, vitamin deficiency, uremia and trichinosis may produce the pattern. Dressler reports 45 cases in which a diagnosis of recent or old myocardial infarction could be made on a basis of clinical and laboratory data. In the remaining 25 per cent there was definite evidence of coronary heart disease.

Currens and Barnes<sup>37</sup> studied the autopsy observations in cases of pulmonary embolism with especial reference to the electrocardiograms. Their paper contains an excellent summary of the factors which influence coronary blood flow in pulmonary embolism. An attempt is made to correlate these factors with the electrocardiographic pattern. They discuss coronary reflex effects, fall of arterial pressure, increase in the heart rate, increase in right ventricular pressure produced by obstruction in the pulmonary circuit (which in turn produces a rise in auricular pressure and in pressure in the coronary sinus) and interference with the coronary venous return to the right ventricle through the thebesian veins. The last two effects are of primary importance in altering the flow of blood through the coronary system.

As far as the electrocardiographic picture was concerned, the authors did not attempt to divide

their tracings into definite groups. In some of the cases there were no electrocardiograms. Thirty cases in which autopsy was done are reported. There was evidence of acute myocardial infarction in 5 of these. One of the 5 patients had a fresh coronary thrombosis, but the other 4 had none.

In conclusion they state

The cause for electrocardiographic changes in pulmonary embolism is considered, and strain on the right ventricle appears to be the determinant factor. The presence of a pulmonocoronary reflex following pulmonary embolism is difficult to prove. It seems likely that compromise in the coronary circulation is best explained by shock and an increase in pressure in the right side of the heart. Decrease in blood flow to the right ventricle from a decrease in arterial pressure gradient, plus an increase in the work of the right ventricle, may account for the occasional association of angina pectoris with pulmonary embolism. Evidence is presented to suggest that asphyxia does not appreciably affect the electrocardiogram in pulmonary embolism.

The importance of using chest leads in the diagnosis of pulmonary embolism is emphasized. Inversion of the T wave in lead CF-2 may be obtained when other leads, including the limb leads, are not diagnostic. Chest leads are of utmost importance to differentiate pulmonary embolism from posterior myocardial infarction.

In this connection it is of interest to refer to the article of Ashman, Byer and Bayley<sup>28</sup> already discussed. They believe that clockwise rotation of the heart around its longitudinal axis as a result of distention of the right side is responsible for the  $S_1$ ,  $Q_3$  abnormalities. Similar patterns are occasionally seen in normal hearts as a result of such rotation, although of course the changes in the T wave are lacking.

Murnaghan, McGinn and White<sup>38</sup> report further studies on the electrocardiogram in cases of pulmonary embolism. They present 10 new cases of acute cor pulmonale with classic changes: (1) presence of, or tendency toward, deviation of the axis to the right, with a prominent S wave in lead I (ST segment may be slightly depressed in this lead), (2) depressed ST take-off in lead II followed by a rising ST segment and a low upright or diphasic T wave, (3) moderately deep Q wave, slight convexity of the ST segment and an inverted T wave in lead III, (4) a diphasic or more often an inverted T wave in lead IV.

Electrocardiographic changes in an additional series of 92 cases of pulmonary embolism are reviewed. Coexistent heart disease occurred in

36 Dressler, W. Myocardial Infarction Indicated by an Electrocardiographic Pattern in Which  $T_1$  Is Lower Than  $T_3$ , *Am Heart J* **26** 313, 1943.

37 Currens, J., and Barnes, A. R. The Heart in Pulmonary Embolism, *Arch Int Med* **71** 325 (March) 1943.

38 Murnaghan, D., McGinn, S., and White, P. D. Pulmonary Embolism With and Without Acute Cor Pulmonale, with Especial Reference to the Electrocardiogram, *Am Heart J* **25** 573, 1943.

69 In 29 symptoms of shock predominated. In 63 signs of pulmonary embolism without shock or collapse were present. Electrocardiographic changes considered indicative of acute cor pulmonale were present in 16 cases of the former group and in 17 of the latter. In other words, the electrocardiogram gave indication of some degree of acute cor pulmonale in a little more than one half of the cases when shock predominated, in a little less than one quarter of the group without shock and in about one third of the entire series, including those cases in which the patients had had abnormal electrocardiograms as a result of heart disease.

The authors again emphasize the importance of pulmonary embolism, especially as a complication of acute or chronic illness of a medical nature. Because of the existing confusion in the literature as to the exact place of the electrocardiogram in the diagnosis of pulmonary embolism, the aim of this paper is to clarify the situation by pointing out that the changes may be pathognomonic in the minority of cases, that nondiagnostic changes may occur, as in the case of myocardial ischemia, particularly in the presence of preexisting heart disease, and, lastly, that in many cases of pulmonary embolism one should not expect to find any electrocardiographic changes at all. It is emphasized again that the terms pulmonary embolism and acute cor pulmonale are not synonymous. The latter occurs only in the presence of a high degree of obstruction (thought to be at least 50 per cent) of the pulmonary circuit.

The authors are in agreement with Wood,<sup>39</sup> who pointed out the importance of taking chest leads over the right side of the heart in making the diagnosis of pulmonary embolism. (Since the publication of the paper by Murnaghan and his associates<sup>38</sup> the taking of multiple chest leads in suspected cases of pulmonary embolism has become routine in the cardiac laboratory at the Massachusetts General Hospital.)

Two cases illustrating the clinical course of potassium poisoning in human beings, with characteristic electrocardiographic changes, are reported by Finch and Marchand.<sup>40</sup> In each case there was an acute uremia with oliguria as the underlying cause and therapeutic administration of potassium salts as a complication. Clinical manifestations include recurrent nausea and retching, episodes of bradycardia unaccompanied by symptoms of cardiac failure or changes in

blood pressure and a sudden ascending flaccid quadriplegia without paralysis of the trunk or disturbances of speech or mental function.

The electrocardiographic changes include elevation of T waves, absence of P waves, intraventricular block and terminal irregularity of the rhythm. Arrest of the heart in diastole prior to cessation of respiration was observed. These findings extended the observations of Winkler, Hoff and Smith,<sup>41</sup> who several years ago defined the electrocardiographic diagnosis of potassium poisoning in man.

Keith, King and Osterberg,<sup>42</sup> in discussing potassium levels in severe renal insufficiency, include an electrocardiogram which shows all of the changes just described.

Brown, Currens and Marchand<sup>43</sup> report 3 interesting cases of muscular paralysis occurring in association with chronic nephritis and having the characteristics of the disability seen in familial periodic paralysis. In these cases it was considered that the paralysis resulted from excessive loss of potassium by the body. Electrocardiographic changes were similar to those observed in periodic paralysis and in depletion of serum potassium from other causes. In all 3 instances the T waves in the electrocardiogram were low and returned to normal with subsidence of the paralysis. Depressed ST segments were also observed, and in one case there was a disturbance of auriculoventricular conduction with Wenckebach periods.

Mazer and Reisinger<sup>44</sup> contribute a study pertaining to changes in the Q wave in the electrocardiogram. The electrocardiographic records of 102 hospitalized patients showing a Q wave in lead III were analyzed. In every instance the Q wave in lead III was at least 25 per cent of the highest R wave in the limb leads. In this group of patients 18.6 per cent had no heart disease. More severe criteria were then applied, and it was discovered that fewer normal persons satisfied them. Among the persons whose records showed Q<sub>3</sub> equal to 100 per cent or more of the highest R wave, only 42 per cent of the patients

41 Winkler, A. W., Hoff, H. E., and Smith, P. K. Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injections of Potassium Chloride, *Am J Physiol* **124** 478, 1938.

42 Keith, N. M., King, H. E., and Osterberg, A. E. Serum Concentration and Renal Clearance of Potassium in Severe Renal Insufficiency in Man, *Arch Int Med* **71** 675 (May) 1943.

43 Brown, M. R., Currens, J. H., and Marchand, J. F. Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, *J A M A* **124** 545 (Feb 26) 1944.

44 Mazer, M., and Reisinger, J. A. Criteria for Differentiating Deep Q-3 Electrocardiograms from Normal and Cardiac Subjects, *Am J M Sc* **206** 48, 1943.

39 Wood, P. Pulmonary Embolism. Diagnosis by Chest Lead Electrocardiography, *Brit Heart J* **3** 21, 1941.

40 Finch, C. A., and Marchand, J. F. Cardiac Arrest by the Action of Potassium, *Am J M Sc* **206** 507, 1943.

with organic heart disease satisfied the criteria, but it is of interest that 16 per cent of the normal subjects were included. Although increasing the severity of the criteria resulted in elimination of more normal subjects, some were still included. Thus it does not appear that such criteria are of great value in assessing the condition in an individual case. It also seems possible that some of the waves designated Q were actually QS deflections.

The effects of digitalis on the electrocardiogram were studied by Dearing, Barnes and Essex<sup>45</sup> as part of an investigation to determine the toxic effect of various preparations of digitalis on the myocardium.<sup>46</sup> With therapeutic doses the changes were minor, consisting of decrease or increase of the height of the T wave in one or more leads or a change in the direction of T<sub>2</sub>. None of the abnormalities described could be considered a reliable index to the presence of a calculated amount of therapeutic digitalis. It was also concluded that the change in heart rate was an unreliable guide.

With toxic doses abnormalities in addition to those just mentioned were seen. These consisted of depression of the RS-T segment in one or more leads, a plus-minus change in the RS-T segment, elevation of the RS-T segment (plateau type) in one or more leads, cove-plane negative T<sub>2</sub> and T<sub>3</sub> with positive T<sub>1</sub>, and positive T<sub>2</sub> and T<sub>3</sub>. The last four anomalies described were associated with definite microscopic myocardial lesions. However, two animals with myocardial lesions failed to show significant changes in their daily electrocardiograms.

Thompson<sup>47</sup> reports a study of the electrocardiographic changes in 25 patients with the hyperventilation syndrome. Abnormalities consisted chiefly of late inversion of the T wave or of depression of the ST segment with marked lowering of the T wave. Any or all leads may be involved. In only 1 case was there a change in the QRS complex, and this was observed in lead 4-F. Neither the degree of alkaline shift nor the extent of lowering of the carbon dioxide-combining power appeared to be the sole factor in determining the kind or magnitude of changes

in ST and T, nor did these changes necessarily depend on changes in the heart rate.

Since severe precordial pain may be included in the syndrome, recognition of these marked electrocardiographic abnormalities is important, lest they be attributed to infarction of the heart.

Ever since the syndrome of bundle branch block associated with short PR interval was described by Wolff, Parkinson and White,<sup>48</sup> a number of theories have been advanced to explain the findings. One of the most popular has assumed the existence of an accessory bundle of conducting tissue (Bundle of Kent) connecting the auricle with the ventricular cavity. Wood, Wolferth and Geckeler<sup>49</sup> present etiologic proof of an accessory muscular connection between auricles and ventricles found at autopsy in a patient with the characteristic Wolff, Parkinson and White syndrome.

Serial histologic sections of a portion of the auriculoventricular groove showed three muscular connections at the right lateral border of the heart between the right auricle and the right ventricle. It was concluded that this furnished further support for the hypothesis of an accessory pathway of auriculoventricular conduction as an explanation for the anomaly. Adequate control studies are still lacking, however.

Fox, Travell and Molofsky<sup>50</sup> report a case in which prolongation of the QRS interval was produced repeatedly by digitalis in a patient whose electrocardiograms taken during the digitalis effect showed a short PR interval with a QRS of characteristic configuration. The QRS interval measured only 0.09 second in the absence of digitalis. The prolongation was abolished by atropine. It is stated that the results of this study are in harmony with the hypothesis favoring an aberrant conduction mechanism. The widening of QRS was thought to be the result of depression of the auriculoventricular node, producing increased activity of the aberrant ventricular conduction tissue, rather than of an action of digitalis on intra-ventricular conduction.

45 Dearing, W. H., Barnes, A. R., and Essex, H. E. Experiments with Calculated Therapeutic and Toxic Doses of Digitalis. II Effects on Electrocardiogram, *Am Heart J* **25** 665, 1943.

46 Dearing, W. H., Barnes, A. R., and Essex, H. E. Experiments with Calculated Therapeutic and Toxic Doses of Digitalis. Effects on Myocardial Cellular Structure, *Am Heart J* **25** 648, 1943.

47 Thompson, W. P. The Electrocardiogram in the Hyperventilation Syndrome, *Am Heart J* **25** 372, 1943.

48 Wolff, L., Parkinson, J., and White, P. D. Bundle-Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *Am Heart J* **5** 685, 1930.

49 Wood, F. C., Wolferth, C. C., and Geckeler, G. D. Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, *Am Heart J* **25** 454, 1943.

50 Fox, T. T., Travell, I., and Molofsky, L. Action of Digitalis on Conduction in the Syndrome of Short PR Interval and Prolonged QRS Complex, *Arch Int Med* **71** 206 (Feb) 1943.



Phang and White<sup>51</sup> report studies on the QT interval in cardiac enlargement. A significant relative prolongation of the QT interval was found in the majority of cases of cardiac enlargement without concomitant congestive failure. It was found that congestive heart failure produced a still greater prolongation. The QT interval showed a relative shortening after recovery from failure, while the patients were still under the influence of digitalis. It was concluded that cardiac enlargement was one of the factors responsible for prolongation of the QT interval, because of the longer pathways of impulse conduction and the greater bulk of contracting muscle. Thus digitalis may affect the duration of systole chiefly by increasing the heart tone, which in turn brings about a decrease in its size.

#### ROENTGENOLOGY

Meneses Hoyos and Quesada<sup>52</sup> studied the cardiovascular roentgen silhouette in normal cadavers by injecting a 50 per cent solution of sodium iodide into large vessels and heart chambers. Roentgenograms were then taken in the posteroanterior, right anterior oblique and left anterior oblique positions. Of special interest were their findings concerning the composition of the left side of the cardiac outline, in view of the past controversy over that point. They concluded that the left side of the outline is made up from above downward of (1) a straight segment corresponding to the left carotid and left subclavian arteries, (2) a middle arch composed of the left division of the pulmonary artery in its upper portion, the main pulmonary artery in its middle portion and the left auricle in its lower portion and (3) the main segment, made up of the left ventricle.

Sussman, Grishman and Steinberg<sup>53</sup> used intravenous injection of 70 per cent diodast to study the problem of right-sided enlargement of the heart. Serial roentgenograms were taken to determine the outline of the great vessels and heart chambers as visualized by the diodast. It was their purpose to reexamine the older criteria for right ventricular enlargement, set

forth by Kirch and summarized by Schwedel<sup>54</sup>. In their analysis of cases of emphysema several persons with normal cardiac configurations by the usual method showed marked right ventricular dilatation when the right ventricle was outlined with the contrast medium. It was shown that the intraventricular septum bulged to the left and the right ventricular apex was widened, neither of which patterns is evident in an ordinary roentgenogram. It was of interest that a bulging right anterior curve in the left oblique position, supposedly a sign of right ventricular enlargement by the old criteria, was encountered only exceptionally.

Angiocardiography in cases of mitral stenosis revealed that the prominent middle left segment seen in the posteroanterior view consisted of the dilated left auricular appendage or atrium in most cases. Thus prominence of the middle segment is not a direct indication of right ventricular enlargement. They found also that the pulmonary artery is not significantly dilated in mitral stenosis but that enlargement of the left auricle may produce elevation of the pulmonary valve and elongation with anterior and cephalad displacement of the pulmonary artery.

In cor pulmonale great dilatation and tortuosity of the pulmonary artery produced a bulge of the middle left cardiac segment. In contrast to the statement found in the old criteria that the outflow tract of the right ventricle contributes to this prominence, it was shown that the pulmonary conus actually did not contribute to the left cardiac contour, although dilatation of the right ventricle produced elevation of the pulmonary artery and contributed to its tortuosity. The authors pointed out that enlargement of the heart to the right with bulging of the right anterior contour in the absence of left ventricular enlargement indicates dilatation of the right auricle in addition to right ventricular involvement. This is said to be of grave prognostic significance because of its usual occurrence in the presence of heart failure.

#### CONGENITAL HEART DISEASE

Keys and Shapiro,<sup>55</sup> faced with the problem of setting up criteria for surgical intervention in cases of patent ductus arteriosus, were stimulated to further investigation into the history of the untreated disorder. It is a common clinical impression that the congenital anomaly of patency of the ductus arteriosus is a comparatively innocuous lesion. In order to determine

51 Phang, S. H., and White, P. D. The Duration of Ventricular Systole as Measured by the Q-T Interval of the Electrocardiogram, with Especial Reference to Cardiac Enlargement With and Without Congestive Failure, *Am Heart J* **26** 108, 1943.

52 Meneses Hoyos, J., and Quesada, J. J. Normal Cardiovascular Roentgen Silhouette, *Arch Int Med* **71** 666 (May) 1943.

53 Sussman, M. L., Grishman, A., and Steinberg, M. F. The Roentgenologic Diagnosis of Right-Sided Enlargement of the Heart, *New England J Med* **228** 777, 1943.

54 Nomenclature and Criteria for Diagnosis of Diseases of the Heart. Criteria Committee of the New York Heart Association, ed 4, New York, New York Tuberculosis and Health Association, 1939.

55 Keys, A., and Shapiro, M. J. Patency of Ductus Arteriosus in Adults, *Am Heart J* **25** 158 1943.



what happens to the older persons with this disability, they analyzed 67 autopsy records from the world literature and from 4 cases of their own. In over 40 per cent of the cases subacute bacterial endarteritis was the cause of death. Twenty-eight per cent of the patients died of congestive failure, and in 2 cases rupture of a pulmonary aneurysm was the final event. After the age of 17 years patency of the ductus arteriosus was associated with an average reduction of life expectancy of about twenty-five years. From this extensive survey it was concluded that "the great majority of patients with this defect suffer no serious disability or restriction of activity during most of their life, but their life expectation is greatly shortened by continued presence of the defect."

In another report the same authors<sup>56</sup> investigated the results of 140 operations submitted by surgeons experienced in the technic. It was shown that the over-all mortality was less than 10 per cent and that in the presence of subacute bacterial endarteritis ligation offers an even chance of survival. It is their opinion that the majority of patients should have ligation performed after careful clinical study, although the danger of development of subacute bacterial endocarditis after successful ligation cannot be properly evaluated as yet. The question of operation in cases of subacute bacterial endarteritis is discussed in another section.

Another factor to be considered when one is contemplating an operation on an older patient is the greater technical difficulty frequently encountered as a result of shortening of the ductus. And in any case there still remains a definite operative risk that must be considered in the case of a person who at the time of operation may be in good health.

Araya and White<sup>57</sup> were interested in the possibility of a relationship between prematurity of birth and congenital cardiovascular defects. Autopsy protocols of prematurely born babies were examined, and only 3 cases (2.2 per cent) of congenital malformation were encountered in a series of 139 autopsies. The incidence of congenital heart disease in relation to prematurity of birth was also investigated. Of 148 patients whose birth weights were normal, 17 weighed less than 2,500 Gm at birth (11.4 per cent). In 172 cases in which the duration of pregnancy was ascertained, 17 infants were born prematurely (9.8 per cent). Thus in cases of con-

genital heart disease the incidence of prematurity of birth was twice that in deliveries of infants with normal hearts. However, only 1 patient out of 19 with patency of the ductus arteriosus, which is in reality a postnatal development, weighed less than 2,500 Gm at birth.

#### BACTERIAL ENDOCARDITIS

Although there are reports of cures in isolated cases of subacute bacterial endocarditis following the use of sulfonamide compounds, with or without adjuvants, this method of therapy on the whole continues to be disappointing.

Lichtman<sup>58</sup> submits a comprehensive report on a total of 704 cases, including 98 of his own and 606 from the literature. The average incidence of recovery was 5.5 per cent. The combination of fever treatment with chemotherapy appeared to offer the best possibilities.

There has been great interest in the possibility that penicillin might prove effective in the treatment of this largely fatal disorder. The commission appointed by the National Research Council on penicillin<sup>59</sup> has submitted a preliminary unfavorable report. Further studies with larger doses are in progress and the results are much more promising, but the duration of the follow-up is far too short for any adequate appraisal.

Loewe, Rosenblatt, Greene and Russell<sup>60</sup> report on a series of 7 consecutive patients apparently treated successfully with a combination of penicillin and heparin. Six patients had underlying chronic rheumatic valvular disease, while the other had a congenital cardiac lesion. *Streptococcus viridans* was the infecting organism in 5, hemolytic streptococci in 1 and pneumococci in 1. The daily dose of penicillin varied from 40,000 to 200,000 Florey units. The dose of heparin averaged about 200 mg daily when given intravenously and 300 mg every second day when given subcutaneously. The results indicated successful sterilization of the blood and relief of clinical manifestations, although admittedly further observations will be required before these patients can be pronounced cured. In no case was the total elapsed time since the beginning of treatment more than one year on the date of publication.

<sup>58</sup> Lichtman, S. S. Treatment of Subacute Bacterial Endocarditis. Current Results, *Ann Int Med* 19: 787, 1943.

<sup>59</sup> Keefer, C. S., Blake, F. G., Marshall, E. K., Lockwood, J. S., and Wood, W. B. Penicillin in the Treatment of Infections, *J A M A* 122: 1217 (Aug 28) 1943.

<sup>60</sup> Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M. Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, *J A M A* 124: 144 (Jan 15) 1944.

<sup>56</sup> Shapiro, M. J., and Keys, A. The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention, *Am J M Sc* 206: 174, 1943.

<sup>57</sup> Araya, E., and White, P. D. The Relationship of Congenital Heart Disease to Premature Birth, *Am Heart J* 25: 449, 1943.

The efficacy of ligation of the patent ductus arteriosus in the treatment of subacute bacterial endarteritis complicating that condition is discussed by Touroff<sup>61</sup>. He reports on a series of 11 patients subjected to operation after the complication of subacute bacterial endarteritis had set in. Two died from complications of operation, and 6 of the 9 survivors recovered without the benefit of chemotherapy. The 3 remaining patients did not recover, in spite of chemotherapy. There was no evidence of preoperative spread of the infection to the cardiac valves or the aorta in any of the 6 who recovered. On the other hand, there was evidence of valvular involvement preoperatively in 3 of those who did not recover. The third was assumed to have had vegetations at the aortic end of the ductus. These observations suggest that operation should be undertaken as soon as a diagnosis of subacute bacterial endarteritis is established. In the present state of development of medical therapy, it may be dangerous to submit the patient to a therapeutic trial of drugs before surgical intervention is attempted.

#### RHEUMATIC HEART DISEASE

Koletsky<sup>62</sup> presents an interesting observation related to the problem of bacterial infection of a bicuspid aortic valve. Congenital heart disease has generally been assigned an important role among the underlying factors concerned with the development of bacterial endocarditis. Bicuspid aortic valve is one of the congenital lesions, along with patent ductus arteriosus and patent interventricular septal defect, which has generally been considered important in this connection. In Koletsky's study 50 adult hearts with bicuspid aortic valve were carefully examined at autopsy, 8 of these showed superimposed bacterial endocarditis. In every specimen of the latter group superimposed bacterial endocarditis involved the bicuspid valves. However, gross changes indicative of rheumatic valvular disease were present on the aortic valves in each instance, including 1 in which a congenital bicuspid lesion was complicated by the rheumatic changes. Of the total of 50 cases of this congenital abnormality, in 40 the disease was acquired and in 10 it was congenital. He concluded that most bicuspid aortic valves in adults are acquired lesions, produced by rheumatic fever. It is the latter, in his opinion, rather than the bicuspid state, which is of importance in the development of bacterial

endocarditis. The article contains a good summary of contributions in the literature bearing on the question of bicuspid valves. Criteria for differentiation are given.

Further evidence is accumulating to show that recrudescence of rheumatic fever may be prevented by the use of sulfonamide drugs. This was well demonstrated in the work of Kuttner and Reyersbach,<sup>63</sup> reviewed in last year's summary of articles on diseases of the heart.<sup>13</sup>

Messelhoff and Robbins<sup>64</sup> used sulfanilamide in daily doses of 20 grains (12 Gm) given to 25 ambulatory rheumatic children. Thirty rheumatic children were used as controls. The patients in the group receiving treatment were observed over two periods of eight months, extending from September to May, and there were 1 recrudescence of rheumatic fever and 2 deaths, 1 from congestive heart failure and 1 from subacute bacterial endocarditis. In the nontreated group 1 patient died from congestive failure and there was one recrudescence of rheumatic fever. From this short series it was not possible to conclude that sulfonamide drugs are especially effective in preventing recurrence of rheumatic fever.

However, the results presented in another report made in 1942 by Hansen, Platou and Dwan<sup>65</sup> are in agreement with the findings of Kuttner and Reyersbach. The consensus among workers in the field is that the method offers definite promise.

Coburn<sup>66</sup> reports his experiences with salicylate therapy in rheumatic fever. It is his belief that the inflammatory reactions of the disease can be suppressed by salicylate therapy, with resultant inhibition of pathologic change in valves and myocardium. The factor of rheumatic infection is apparently not modified by therapy. A simple method for the determination of the salicyl radical is described, providing more effective therapeutic control through measurement of blood levels of the drug. The intravenous use of sodium salicylate is advocated in the first stages

63 Kuttner, A. G., and Reyersbach, G. The Prevention of Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, *J Clin Investigation* **22** 77, 1943.

64 Messelhoff, C. R., and Robbins, M. H. The Prophylactic Use of Sulfanilamide in Children with Rheumatic Heart Disease, *J Lab & Clin Med* **28** 1323, 1943.

65 Hansen, A. E., Platou, R. V., and Dwan, P. F. Prolonged Use of a Sulfonamide Compound in Prevention of Rheumatic Recrudescence in Children. An Evaluation Based on a Four Year Study on Sixty-Four Children, *Am J Dis Child* **64** 963 (Dec) 1942.

66 Coburn, A. F. Salicylate Therapy in Rheumatic Fever. A Rational Technique, *Bull Johns Hopkins Hosp* **73** 435, 1943.

61 Touroff, A. S. W. The Results of Surgical Treatment of Patency of the Ductus Arteriosus Complicated by Subacute Bacterial Endarteritis, *Am Heart J* **25** 187, 1943.

62 Koletsky, S. Bicuspid Aortic Valves and Bacterial Endocarditis, *Am Heart J* **26** 343, 1943.

of active rheumatic infection. Further evaluation is needed, and the possibility of severe toxic reactions must be kept in mind. The drug may have a profound effect on body metabolism in larger doses.<sup>67</sup>

#### HYPERTENSION

Investigation of the problem of hypertension by the experimental approach, with especial reference to a humoral mechanism of renal origin, continues to need follow-up. It is impossible to attempt a comprehensive review of this complex subject in a brief article.

Page and co-workers<sup>68</sup> have published a progress report of the experimental treatment of hypertension with renal extracts, in which the concept that renal ischemia is not essential to the production of hypertension is reiterated. Reduction of renal pulse pressure is thought to be a more essential mechanism. Improvement in the quality of renal extracts has been achieved, in that reactions have been reduced, but as yet the yield of active substance is low. An *in vitro* method for assay of renal extract has been developed, which depends on the ability of the extract to destroy angiotonin. However, it has also been observed that with reduction in severity of reaction antipressor activity has also been lessened. The author still supports the concept of a humoral mechanism in which kidney substance, renin, interacts with renin activator to produce an effective vasoconstrictor agent, angiotonin.

Further studies have been carried out to show that this vasoconstrictor substance exhibits properties similar to those seen in hypertension. This is reported in detail in an article by Taylor and Page,<sup>69</sup> in whose experiments the reaction of the cardiovascular system in human beings was measured by the ballistocardiograph. Angiotonin administered to patients with normal cardiovascular systems reduced the stroke volume and cardiac output as measured by that instrument. On the other hand, when the antipressor angiotonin-destroying renal extract was given to hypertensive patients, the cardiac output increased and the contour of the curve bore a closer resemblance to the normal. These findings dif-

fered from those obtained with other pressor substances (methyl guanidine or tyramine).

In the progress article already mentioned, Page and his associates<sup>68</sup> state that clinical results obtained with the antipressor renal extract in 37 patients continue to be encouraging. Twenty-four of these had malignant hypertension, and 9 died. Reversal of changes in the eyegrounds with improvement of vision, reversal of the abnormal electrocardiographic picture to a more normal pattern and decrease in diastolic blood pressure with increase in cardiac output were the most striking changes in the group with malignant hypertension.

Plentl and Page<sup>70</sup> studied the nature of renin and angiotonin by means of a kinetic analysis of the renin-angiotonin pressor system. For a more complete account of the work on the subject of the mechanism of the production of hypertension done during the past year, reference should be made to various articles.<sup>71</sup>

Lisa, Eckstein and Solomon<sup>72</sup> describe the condition of the main renal arteries in 100 consecutive patients coming to autopsy at the City Hospital, Welfare Island, New York. Studies were carried out on tissues in the fresh state to eliminate the error produced by shrinkage with fixation. There were 56 hypertensive subjects and 44 without hypertension. The differences in caliber between the sclerotic vessels in the two groups were insignificant, and the authors concluded that arteriolar sclerosis is a better index of blood pressure than the caliber of the

70 Plentl, A. A., and Page, I. H. A Kinetic Analysis of the Renin-Angiotonin Pressor System and the Standardization of the Enzymes Renin and Angiotoninase, *J. Exper. Med.* **78** 367, 1943.

71 (a) Leiter, L., and Eichelberger, L. Duration of Pressor Effect of Large Doses of Renin (Kidney Extract) in Conscious Normal and Renally Abnormal Dogs. Observations on Anesthetized and Uremic Dogs and Anaphylactic and Pathological Effects of Pig Renin, *J. Clin. Investigation* **22** 11, 1943. (b) Plentl, A. A., and Page, I. H. Enzymatic Nature of Angiotonin Formation from Renin (Kidney Extract) and Renin Activator, *J. Biol. Chem.* **147** 135, 1943. (c) Page, I. H. Newer Concepts of Mechanism of Arterial Hypertension, *J. Omaha Mid-West Clin. Soc.* **4** 23, 1943. (d) White, B. V., Durkee, R. E., and Mirabile, C. Renal Hypertension. Review of the Status, Including Report of a Case of Hypertension Relieved After Nephrectomy, *New England J. Med.* **228** 277, 1943. (e) Goldblatt, H., Katz, Y. J., Lewis, H. A., and Richardson, E. Bioassay of Renin (Kidney Extract), *J. Exper. Med.* **77** 309, 1943. (f) Grollman, A., Harrison, T. R., and Williams, J. R. Mechanism of Experimental Renal Hypertension in the Rat. Relative Significance of Pressor and Antipressor Factors, *Am. J. Physiol.* **139** 293, 1943.

72 Lisa, J. R., Eckstein, D., and Solomon, C. Relationship Between Arteriosclerosis of Renal Artery and Hypertension. Analysis of One Hundred Necropsies, *Am. J. M. Sc.* **205** 701, 1943.

67 Barnett, H. L., Powers, J. R., Benward, J. H., and Hartmann, A. F. Salicylate Intoxication in Infants and Children, *J. Pediat.* **21** 214, 1942.

68 Page, I. H., Helmer, O. M., Kohlstaedt, K. G., Kempf, G. F., Corcoran, A. C., and Taylor, R. D. Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts, *Ann. Int. Med.* **18** 29, 1943.

69 Taylor, R. D., and Page, I. H. The Effect of Antipressor Kidney Extract, Angiotonin (etc.) on Cardiac Output as Measured by the Ballistocardiograph in Hypertensive and Normal Persons, *Am. J. M. Sc.* **205** 66, 1943.

main renal arteries. They believe that gross reduction of blood flow resulting from arteriosclerosis of the main renal arteries is of less importance than lowering of pulse pressure within the kidney.

One of the circumstances which has hampered the investigation of hypertension in human beings is the fact that most of the autopsy material has been obtained from patients with hypertension of long standing. Opportunities to study the histologic changes in the kidney in early hypertension have been few. The pioneer investigations of Castleman and Smithwick<sup>73</sup> in this direction are of much importance. In the course of bilateral extensive splanchnic denervation (sympathectomy) done on 100 hypertensive patients, renal biopsies were made. This group included persons with all degrees of the hypertensive state, with changes in the eyegrounds varying from arteriolar narrowing or constriction without nicking (grade I) to edema of the optic disks with measurable elevation, usually accompanied by hemorrhage, exudate and other abnormalities (grade IV). Fourteen per cent of the subjects showed changes of grade IV. The average findings in the series were blood pressure, 210 systolic and 130 diastolic, age, 39, duration, six years. The renal function as measured by the phenolsulfonphthalein test was normal in 60 per cent of the subjects. Insignificant or no vascular renal disease was evident in 28 per cent of the biopsies, and only mild changes occurred in an additional 25 per cent.

It was concluded that "the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing hypertension, and that in many of these and probably others the hypertensive state antedated the renal vascular lesion, which, once established, probably aggravated the hypertension. Furthermore, these observations are not in keeping with the concept that renal ischemia due to preexisting renal vascular disease is the cause of essential hypertension in man."

Talbott and Castleman and co-workers<sup>74</sup> correlated the observations in renal biopsies with results of studies of renal clearance done on 20 patients with essential hypertension. It was

73 Castleman, B., and Smithwick, R. H. The Relation of Vascular Disease to the Hypertensive State Based on a Study of Renal Biopsies from One Hundred Hypertensive Patients, *J. A. M. A.* **121** 1256 (April 17) 1943.

74 Talbott, J. H., Castleman, B., Smithwick, R. H., Melville, R. S., and Pecora, L. J. Renal Biopsy Studies Correlated with Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy, *J. Clin. Investigation* **22** 387, 1943.

discovered that the glomerular filtration rate and the renal blood flow were most significantly reduced in the patients who showed the most advanced changes of renal vascular disease by biopsy. They found the filtration fraction normal in 7 of 8 patients in the group showing late or no pathologic change in the kidneys. The authors believed that the observations indicated that constriction of the efferent glomerular arterioles was not present in the early stages of renal vascular disease. Lumbodorsal splanchnicectomy had little effect on renal clearance when measured in the horizontal position.

An important approach to the present day treatment of hypertension is surgical splanchnic denervation. The extensive operation of dorso-lumbar sympathectomy developed by Smithwick and previously reported<sup>75</sup> has been in continued use by this author at the Massachusetts General Hospital in the treatment of hypertension. The details of this work are as yet unpublished, but the clinical results in selected cases are impressive, with regard both to lowering of the blood pressure, systolic and diastolic, and to subjective improvement.

An interesting report was made by Friedman and Kasanin,<sup>76</sup> who described the occurrence of hypertension in one of identical twins with definite evidence of disease of the coronary arteries shown by the electrocardiogram and by clinical findings. The other twin had a normal blood pressure and electrocardiogram. Both had a diminished renal blood flow as compared with the average value of 1,280 cc per minute. In the patient with hypertension the flow as calculated was 606 cc per minute, while in the normal brother the figure was 725 cc per minute. Difference in personality was striking. The descriptive terms dynamic, aggressive, energetic, active and successful were applied to the twin with high blood pressure, while the normal brother was more alert mentally and stronger physically but lacking in "drive." No conclusions are drawn, but it is suggested that a possible cause of the hypertension may lie in the divergent personality trends, especially in view of the similarity in heredity and early environment. Because of the fact that the renal blood flow was somewhat reduced in the so-called normal twin, it will be of interest to see if he also eventually has hypertension.

75 Smithwick, R. H. A Technic for Splanchnic Resection for Hypertension, *Surgery* **7** 1, 1940.

76 Friedman, M., and Kasanin, J. S. Hypertension in Only One of Identical Twins, *Arch. Int. Med.* **72** 767 (Dec.) 1943.

## CORONARY HEART DISEASE

Askey,<sup>77</sup> in reviewing the syndrome of painful disability of the shoulder and hand following coronary occlusion, suggests that some of the changes in the palmar aponeurosis may be related to myocardial infarction. Moreover, Kehl<sup>78</sup> reports 6 cases of Dupuytren's contracture following coronary occlusion within a period of eleven months. In no case was there any evident relationship to trauma or any change before the thrombosis occurred. Pain, stiffness, swelling, repeated discoloration, numbness, tingling and coldness of the hands were encountered with the contracture. Four of the patients also had pain in the shoulder. Johnson<sup>79</sup> reports clinical observations in 39 cases in which disabling changes in the hands resembling sclerodactylia followed myocardial infarction. In a period varying from three to sixteen weeks after infarction occurred, pain and stiffness of the fingers appeared, with nonpitting swelling of the hands. Evidence of circulatory change was seen in the form of coldness and change in color, which varied from erythema to cyanosis. At a later date thickening of the skin, atrophy of the soft tissue and in some cases palmar contracture occurred. The changes described bore a close resemblance to the sclerodactylia of scleroderma and Raynaud's disease. The "anginal syndrome" was present in every case. Pain in the shoulder occurred in 34 patients and bore some relation to the site of radiation of anginal pain. The changes in the hand were bilateral. Arthritis did not appear to be an important factor in the genesis of this syndrome. Although 10 patients had a brief "rheumatic" history, none had had previous rheumatoid arthritis, and 4 had had hypertrophic arthritis. It is emphasized that the changes described do not progress to gangrene and trophic ulceration of the fingers, in spite of their resemblance to the sclerodactylia of Raynaud's disease. The possible etiologic relationships are discussed.

Starr and Wood<sup>80</sup> used the ballistocardiogram to study the circulation in patients with coronary artery disease, including acute myocardial in-

farction and chronic angina pectoris. One hundred and six observations were made on 55 patients having those diseases. Measurements of the circulation with the ballistocardiograph were either normal or below normal in the acute period after infarction. In the first instance the circulation tended to diminish and reached a minimum between the third and the fifth week, with later recovery. In the great majority of cases of chronic coronary disease with angina of effort the circulation was abnormal. Abnormalities of form in the tracing were frequently encountered in association with coronary heart disease. Limitations of this method are manifested with regard to the diagnosis of anatomic lesions. The measurements gave objective aid in making the diagnosis but should be regarded as of the same order of significance as measurements of blood pressure, etc.

Master, Jaffe, Dack and Silver<sup>81</sup> followed the course of the blood pressure in 538 cases of coronary occlusion over an average period of three and a half to four years (range, one to seven years). In every case the blood pressure fell to some extent, although the occurrence of a transitory rise at the beginning was observed in a few. The lowest pressure was usually reached between the twelfth and the twentieth day. In comparing the data for the hypertensive and the nonhypertensive subjects it was observed that the blood pressure trend was similar, although among the nonhypertensive patients who died a rapid fall was more common. Two thirds of the hypertensive patients regained a hypertensive level, but one half of this group showed a delayed rise over a period of one to two years. It was concluded that the height of the blood pressure after the attack did not influence the future course of the patient significantly with respect to subsequent angina pectoris, heart failure, coronary occlusion or death.

White, Bland and Miskall<sup>82</sup> have collected important data relating to the prognosis of angina pectoris. It is their contention that the only accurate basis for prognosis in that disease is a long time follow-up of a large group of patients through the entire course of the disease. Their report consists of a further follow-up of 497 patients with angina pectoris first observed in

77 Askey, J. M. The Syndrome of Painful Disability of Shoulder and Hand Complicating Coronary Occlusion, *Am Heart J* **20** 1, 1941.

78 Kehl, K. C. Dupuytren's Contracture as a Sequel to Coronary Artery Disease and Myocardial Infarction, *Ann Int Med* **19** 213, 1943.

79 Johnson, A. C. Disabling Changes in the Hands Resembling Sclerodactylia Following Myocardial Infarction, *Ann Int Med* **19** 433, 1943.

80 Starr, I., and Wood, F. C. Studies with Ballistocardiograph in Acute Cardiac Infarction and Chronic Angina Pectoris, *Am Heart J* **25** 81, 1943.

81 Master, A. M., Jaffe, H. I., Dack, S., and Silver, N. The Course of the Blood Pressure Before, During, and After Coronary Occlusion, *Am Heart J* **26** 92, 1943.

82 White, P. D., Bland, E. F., and Miskall, E. W. The Prognosis of Angina Pectoris. A Long Time Follow-Up of 497 Cases, Including a Note on 75 Additional Cases of Angina Pectoris Decubitus, *J A M A* **123** 801 (Nov 27) 1943.



the years from 1920 to 1930<sup>83</sup> Of this number 445 patients were dead and 52 were living The average duration of life of the dead patients was seven and nine-tenths years after the onset of symptoms, while for the 52 living patients the average duration of the disease was eighteen and four-tenths years The average for both living and dead patients is nine years to date, which is considerably higher than the "classic and often quoted figure of five years" The factors of hypertension, myocardial infarction, cardiac enlargement, abnormal heart sounds, congestive failure and abnormal electrocardiogram occurred much more frequently in the group of patients who died within three years than in the 52 patients still living The authors also inquired into the prognostic significance of angina pectoris decubitus, which was present in 20 per cent of the total number

Much has been written in recent years concerning the mechanism of production of coronary occlusion, and it has been held that bleeding from vascular channels of the intima of a vessel may cause arterial occlusion, either directly by producing local hematoma or indirectly by thrombus formation near the site of the hemorrhage

English and Willius<sup>84</sup> investigated this question by means of autopsy studies One hundred and thirty-five selected hearts were examined, 40 per cent of which showed intimal hemorrhage There was acute occlusion of the coronary artery in 20 specimens Wherever hemorrhage was encountered in the intima of a coronary artery, coexistent degenerative changes were found It was concluded that the intimal degenerative changes represented the primary factor in the pathologic condition, while the hemorrhage was secondary

Steiner and Domanski<sup>85</sup> studied the serum cholesterol level in 15 patients with coronary heart disease and in 15 controls of the same age They made repeated observations over periods up to two years The level in the patients with coronary arteriosclerosis was found significantly higher than that in the normal subjects, with wide fluctuations characterizing the former group and fairly constant levels occurring in the latter group

83 White, P D, and Bland, E F A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis A Study of 500 Cases of the Former Condition, and of 200 Cases of the Latter, *Am Heart J* 7 1, 1931

84 English, J P, and Willius, F A Hemorrhagic Lesions of the Coronary Arteries, *Arch Int Med* 71 594 (May) 1943

85 Steiner, A, and Domanski, B Serum Cholesterol Level in Coronary Arteriosclerosis, *Arch Int Med* 71 397 (March) 1943

Engelberg and Newman<sup>86</sup> have reported 6 instances of disease of the coronary arteries in young adults with xanthomatosis In each case three characteristic features were present The cutaneous lesions consisted of single or multiple firm subcutaneous nodules of variable size, found mostly on the extensor surfaces of the extremities In every case the diagnosis of coronary insufficiency was made, and all the patients showed hypercholesteremia The results of treatment with low cholesterol diet were inconclusive Only 3 of the patients followed the diet faithfully, and in only 1 was there a marked fall in the blood level (430 to 290 mg per hundred cubic centimeters)

Massie and Miller<sup>87</sup> determined the size and shape of the heart by roentgenography in 16 patients who had had myocardial infarction Films were taken at the bedside with patients in the sitting position on the third, fifth, twelfth and twenty-eighth days and during the third and sixth months No consistent change in cardiac size was observed In the two weeks following the infarction only 4 patients showed a demonstrable alteration in the size of the heart, which was increased in 2 and decreased in the other 2 Eight patients showed no change in the six month period The alterations observed in the pulmonary fields were of interest in that 12 patients showed pulmonary congestion in the first one to two weeks, with the presence of basal rales by auscultation in only 7

Many patients with angina pectoris complain of characteristic substernal oppression in the absence of the usual precipitating factors In some a reflex mechanism initiated by disease in the gastrointestinal tract (cardiospasm, hiatus hernia, disease of the gallbladder, ulcer) can be demonstrated

Harrison and Finks<sup>88</sup> present evidence to show that disturbed carbohydrate metabolism is another disorder which may precipitate various manifestations referable to the cardiovascular system Characteristic features of such a mechanism are the appearance of symptoms two or more hours after meals, with relief following the injection of dextrose, and reproduction of symptoms following administration of insulin The

86 Engelberg, H, and Newman, B A Xanthomatosis A Cause of Coronary Artery Disease in Young Adults, *J A M A* 122 1167 (Aug 21) 1943

87 Massie, E, and Miller, W C The Heart Size and Pulmonary Findings During Acute Coronary Thrombosis, *Am J M Sc* 206 353, 1943

88 Harrison, T R, and Finks, R M Glucose Deficiency as a Factor in the Production of Symptoms Referable to the Cardiovascular System, *Am Heart J* 26 147, 1943



authors refer to the state which produces these symptoms as "relative hypoglycemia," because the blood sugar values of the patients studied were usually within the limits of normal or only slightly abnormal. In many cases studied the subjective and objective reactions were similar to those commonly seen in cardiac neurosis. However, attacks of angina pectoris at rest were seen in those with typical effort angina.

Lesser<sup>89</sup> reports further observations on the action of testosterone propionate in the treatment of angina pectoris. Favorable results were obtained in every one of 22 patients with angina. A control series of patients who received sesame oil showed no improvement. After treatment was initiated, an average of twenty-eight days elapsed before improvement was noted, and a period of forty-three days elapsed before this became marked.

On the other hand, Levine and Likoff,<sup>90</sup> after a trial of the drug in 19 patients, were unable to conclude that it had any beneficial effect. Five of the 19 patients observed reported definite improvement, but the authors believed that this could be accounted for by the vagaries of the disease. Eleven patients reported no change whatever after four weeks of treatment with a dose of 25 mg three times weekly.

#### CONGESTIVE HEART FAILURE

Although the clinical manifestations of congestive heart failure are well known, the exact mechanism of production is still a matter of controversy. Evidence is accumulating to discount as the only factor a simple mechanical basis for heart failure, in which peripheral venous congestion is said to indicate disproportionate failure of the right ventricle.

Starr, Jeffers and Meade<sup>91</sup> report results of acute and chronic experiments on the right side of the heart in dogs in which only slight changes of venous pressure followed extensive damage to the right side of the heart. In the acute experiments the right ventricle was damaged with a cautery, and in the chronic experiments vessels supplying the right side of the heart were ligated. They concluded that the

mechanical factors directly connected with weakness of the right side of the heart are less important in the production of elevated venous pressure than tone of the blood vessels and other factors concerned with blood volume. It is hardly necessary to point out that the results of these experiments on animals are not wholly transferable to human patients.

Further observations on this problem carried out on human beings are reported by Warren and Stead,<sup>92</sup> in which peripheral accumulation of fluid in heart failure was observed before the venous pressure rose above normal levels. Both articles stress the fact that the knowledge of the dynamics of venous congestion in man is still far from complete.

Fahr and Buehler<sup>93</sup> attempted accurate quantitative definition of acute congestive heart muscle failure in physiologic terms. Their studies were carried out on heart-lung preparations. Their conclusions, in some contrast to those of Starr, Jeffers and Meade,<sup>91</sup> were

The cardinal features of spontaneous heart failure or that produced by chloroform, chloral hydrate, alcohol and diphtheria toxin are (a) a decrease in mechanical efficiency of the heart, (b) dilatation of the ventricles, (c) a rise of the venous pressure in the right and left auricles, (d) a tendency toward decrease in the minute output of the ventricles.

All of the articles reviewed in this section contain a discussion of these controversial points and references for suggested reading.

LaDue and Fahr<sup>94</sup> investigated the effect of intravenous administration of lanatoside C on heart failure in the presence of normal sinus rhythm in human beings. Kymographic measurements of the size of the heart were made by the method of Keys and Friedell.<sup>95</sup> The limitations of this method are recognized, that is, the stroke volume of the left ventricle may not be numerically exact, but it is felt that reliable indexes of direction or magnitude of any change in the output of the heart can be obtained by

89 Lesser, M. A. Treatment of Angina Pectoris with Testosterone Propionate, *New England J Med* **228** 185, 1943.

90 Levine, S. A., and Likoff, W. B. The Therapeutic Value of Testosterone Propionate in Angina Pectoris, *New England J Med* **229** 770, 1943.

91 Starr, I., Jeffers, W. A., and Meade, R. H. The Absence of Conspicuous Increments of Venous Pressure After Severe Damage to the Right Ventricle of the Dog, with a Discussion of the Relation Between Clinical Congestive Failure and Heart Disease, *Am Heart J* **26** 291, 1943.

92 Warren, J. V., and Stead, E. A. Fluid Dynamics in Chronic Congestive Heart Failure. An Interpretation of the Mechanisms Producing the Edema, Increased Plasma Volume, and Elevated Venous Pressure in Certain Patients with Prolonged Congestive Failure, *Arch Int Med* **73** 138 (Feb) 1944.

93 Fahr, G., and Buehler, M. S. A Physiologic Definition of Acute Congestive Heart Muscle Failure, *Am Heart J* **25** 211, 1943.

94 LaDue, J. S., and Fahr, G. The Effect of the Intravenous Administration of Lanatoside C upon the Output, Diastolic Volume, and Mechanical Efficiency of the Failing Human Heart, *Am Heart J* **25** 344, 1943.

95 Keys, A., and Friedell, H. Measurement of the Stroke Volume of the Human Heart from Roentgenograms. Simultaneous Roentgenkymographic and Acetylene Rebreathing Experiments, *Am J Physiol* **126** 741, 1939.

successful estimations of output from kymograms. The diastolic volume of normal and pathologic hearts can be ascertained accurately. The authors state

The intravenous administration of lanatoside-C to patients with heart failure and normal sinus rhythm usually increases the pulse pressure and reduces circulation time and venous pressure within two hours. In ten such patients the diastolic heart volume was reduced in five and stroke volume was increased in eight. In the latter eight the product of the stroke output and the mean blood pressure was definitely increased, whereas the diastolic heart volume decreased or was unchanged. Since the latter is an index of oxygen consumption, these increases in work must have meant improvement in the mechanical efficiency of the hearts of eight out of the ten patients studied.

#### WAR MEDICINE

A large scale experiment has been carried out in the reexamination of 4,994 men rejected for military service because of the diagnosis of cardiovascular defects or neurocirculatory asthenia.<sup>96</sup> It is necessary to quote the conclusions almost in their entirety because of the complex nature of the study.

2 The chief reasons for the reexamination were to determine (a) the problems in cardiovascular diagnosis that particularly concern the range of the normal cardiovascular system with respect to service, (b) the possible salvage of men for the Army by reclassification as 1A, and (c) the comparison of opinions of cardiovascular experts with those of the examiners at local boards and induction stations to determine the desirability of such reexaminations in this or other special medical fields throughout the country.

3 Of the total number of 4,994 cardiovascular rejectees examined, there were 863 (17.3 per cent) resubmitted as 1A and 4,131 (82.7 per cent) whose rejection as 4F was confirmed.

4 The percentage of men resubmitted as 1A was quite similar in Boston (18.8 per cent),<sup>97</sup> New York (19.2 per cent), and Philadelphia (16.5 per cent). In San Francisco 28.6 per cent were resubmitted.<sup>98</sup> Chicago yielded the lowest salvage (3.88 per cent), apparently because of the fact that cardiovascular experts had already been freely used in the decision about doubtful cases, a procedure which might profitably be followed by other examining groups throughout the country.

5 The chief cause for rejection was rheumatic heart disease, found in 2,476 men, or 50 per cent of the

total 4,994, and in 59.9 per cent of the final 4F group. Mitral valvular disease without aortic valvular disease was diagnosed in the majority of these rheumatic heart cases, 1,500, or 60.6 per cent (750 with obvious stenosis), aortic valvular disease without apparent mitral valve involvement in 280, or 11.3 per cent (72 aortic stenosis and 208 aortic regurgitation alone), and mitral and aortic valvular disease combined in the remaining 628, or 25.4 per cent. Auricular fibrillation complicating mitral stenosis was found in 24 of the cases. The incidence of rheumatic heart disease varied from 70.3 per cent of the rejectees in Chicago to 39.6 per cent in San Francisco.

6 The second most common cause for final rejection was hypertension, found in 1,059 cases (25.6 per cent of the 4F cases and 21 per cent of the total series). The majority showed elevation of both systolic and diastolic levels, a few had either systolic hypertension alone or diastolic hypertension alone. The incidence varied little from city to city but was relatively more common in the fourth than in the third decade.

7 Third in frequency as a cause of rejection was neurocirculatory asthenia with 204 cases (4.0 per cent of the total series, or 4.9 per cent of those finally labeled 4F). Negroes were rarely affected. The incidence varied from 7.8 (8 per cent) in Boston to 1.1 (1.1 per cent) in Chicago.

8 The fourth condition responsible for rejection of more than 100 men was sinus tachycardia, there were 189 cases, or 3.8 per cent of the entire group and 4.6 per cent of the final 4F cases. The numbers varied from 75 in Chicago to 8 in Philadelphia.

9 The fifth most common cause for rejection was congenital heart disease, found in 183 cases (4.4 per cent of the 4F cases). The abnormality most commonly diagnosed was ventricular septal defect (Roger's disease) in more than a third of all the cases, 73. Five other defects, in the order of their frequency, were patency of the ductus arteriosus (29 cases), pulmonary stenosis (13 cases and 2 more with the tetralogy of Fallot), coarctation of the aorta (14 cases), auricular septal defect (6 cases) and subaortic stenosis (5 cases). The city incidence varied from over 6 per cent (63 cases) in San Francisco to 1.8 per cent (18 cases) in Philadelphia.

10 Other causes for rejection include cardiac enlargement alone, determined by x-ray examination (76 cases), arrhythmia in 32, including 17 cases of paroxysmal tachycardia, 6 of uncomplicated auricular fibrillation, 2 of auricular flutter and 5 of auriculoventricular block, electrocardiographic abnormalities alone in another 32 cases including 10 with bundle branch block, cardiovascular syphilis in only 17 cases, thyrotoxicosis in 14, recent rheumatic fever in 13, cardiac strain from chest deformities in 10, coronary heart disease in only 6, pericarditis in 4, and peripheral vascular defects in 3. Unspecified heart disease was diagnosed in 113 cases.

11 A history of rheumatic fever was obtained in slightly over a fourth of all the cases of rheumatic heart disease (28.8 per cent in four of the cities) and in nearly half of those in Boston and New York. A history of chorea was rare (1.8 per cent of the rheumatic heart cases in these same four cities).

12 Although the great majority reexamined were white men there were a good many Negroes (something under 10 per cent, 386 out of 4,035 examined in four of the five cities) and a few Chinese and Filipinos. There was a high rejection rate for the Chinese and Filipinos (100 per cent) in the four cities in which racial data were available. Nine of the fifteen cases of

<sup>96</sup> Levy, R. L., Stroud, W. D., and White, P. D. Report of Reexamination of 4,994 Men Disqualified for General Military Service Because of the Diagnosis of Cardiovascular Defects. A Combined Study Made by Special Medical Advisory Boards in Boston, Chicago, New York, Philadelphia and San Francisco, *J. A. M. A.* **123**: 937 (Dec 11), 1029 (Dec 18) 1943.

<sup>97</sup> "Another 11.4 per cent were considered 'borderline' in Boston but after special consideration were not resubmitted."

<sup>98</sup> "The men resubmitted in San Francisco included a moderate number of 'borderline' cases, while in Chicago, New York and Philadelphia the majority of 'borderline' cases were rejected again."

aortic syphilis found in those cities were among Negroes, and hypertension was also more often found in the Negroes (38.5 per cent of the final 4F cases compared to 23.1 per cent for the white men). Rheumatic heart disease was evenly represented (63.8 per cent compared to 63.9 per cent), but neurocirculatory asthenia was very much less in the Negroes (0.9 per cent, compared to 5.5 per cent).

13 There were eight problems of particular interest which remain unsolved and should be the focus of follow-up study but concerning which tentative opinions were expressed: (a) the interpretation of apical systolic murmurs (may they, if very slight or even slight, in the absence of any other abnormal or doubtful finding, be considered inadequate reason for rejection?), (b) the upper limits of the normal blood pressure (may the systolic pressure in very nervous young men be set perhaps as high as 160 mm of mercury or even a shade more, provided the diastolic pressure does not exceed 90 mm?), (c) the limits of the normal pulse rate at rest (may there not be a wider range, say from 40 to 120 per minute, than that actually given in the current criteria?), (d) the heart size, which also varies widely, especially according to body build, and may perhaps in a few normal individuals exceed the standards set by Hodges and Eyster, (e) the electrocardiogram, of which the wide range of normal has not yet been explored adequately, (f) neurocirculatory asthenia, difficult to diagnose in mild degree, but probably rejectable even when slight, unless there is an obvious cause which can be corrected, (g) recent rheumatic fever, a hazard even when the heart seems perfectly normal, and (h) exercise tests, the usefulness of which, in cardiovascular examination for military service, is open to question.

14 A follow-up study of the men reclassified as 1A and especially of the doubtful "borderline" cases in the final 4F group should, in the years to come, aid in solving some of the various problems in cardiovascular diagnosis that still remain.

15 The wisdom of extending these reexaminations for the sake of the salvage alone is doubtful in view of the time required, the few expert examiners available, and the relatively small percentage of men reclassified as 1A, but the applications of the lessons learned in the course of this study should be helpful in future examinations.

Follow-up observations from New York, Boston and Chicago indicate that most of the men recommended as suitable for service with the armed forces have been inducted into service.

Several important papers relating to cardiovascular disease in wartime will appear during 1944.

#### MISCELLANEOUS

Gouley and Sickel<sup>99</sup> report a series of cases in which the pathologic observations point to a cause for aortic regurgitation which hitherto has not been stressed, although it has not escaped recognition. They comment on the occurrence of aortic regurgitation in patients in the older

age groups, in whom syphilis, rheumatic heart disease, bacterial endocarditis or arteriosclerotic degeneration is not the etiologic factor. The 11 patients whose cases are reported showed the characteristic diastolic murmur of aortic regurgitation. Hypertension was present in most cases. The pathologic factors consisted of dilatation of the aortic ring with a characteristic valvular lesion consisting of sclerotic thickening of the midportion of the free margin of the leaflet without involvement of the commissures. The latter may be pulled apart, and the leaflets are frequently elongated. These changes are considered secondary to dilatation of the ring and are effected by the eroding action of flow leakage. Syphilis may coexist.

Weiss, Stead, Warren and Bailey<sup>100</sup> express the belief that scleroderma heart disease is a clinical and pathologic entity. Nine cases of generalized scleroderma were reported, with signs and symptoms of heart disease in each. Good evidence to show that none of the common etiologic factors contributed to the heart failure was presented. Autopsy observations (2 cases) were of special interest, in that scars of unusual type involving the myocardium primarily were found. These differed from ordinary vascular lesions in absence of significant abnormalities in the vessels, lack of hemosiderin deposits, inconstant relation to arteries and an unusual cellular character of the connective tissue itself. The frequent association of pulmonary lesions made the evaluation of cardiac symptoms difficult. All patients showed cardiac enlargement, dyspnea and edema. The electrocardiograms were abnormal in each case without consistent diagnostic patterns. It was concluded that in generalized scleroderma the heart, as well as the lungs and the gastrointestinal tract, may be involved.

Smith and Furth<sup>101</sup> report 5 cases of congestive failure of obscure origin in which the findings were similar to those in previously reported instances of Fiedler's myocarditis. Endocardial and myocardial fibrosis with cardiac hypertrophy and dilatation without change in the vessels or valves characterized the postmortem picture. In 3 cases mural thrombi were present, and in all cases widespread endocardial fibrosis in both ventricles was found. Because of a history of

<sup>100</sup> Weiss, S., Stead, E. A., Jr., Warren, J. V., and Bailey, O. T. Scleroderma Heart Disease, *Arch Int Med* **71** 749 (June) 1943.

<sup>101</sup> Smith, J. J., and Furth, J. Fibrosis of the Endocardium and the Myocardium with Mural Thrombosis, *Arch Int Med* **71** 602 (May) 1943.

<sup>99</sup> Gouley, B. A., and Sickel, E. M. Aortic Regurgitation Caused by Dilatation of the Aortic Orifice and Associated with a Characteristic Valvular Lesion, *Am Heart J* **26** 24, 1943.

dietary deficiency in each instance the possibility of beriberi heart disease was considered, but no patient responded to thiamine chloride. Need for further definition of myocarditis of obscure origin is recognized.

Carter and Traut<sup>102</sup> investigated the incidence of angina pectoris in 300 patients with proved pernicious anemia. In only 3 could a definite diagnosis of angina be made. They were also interested in the incidence of symptoms and findings suggesting organic heart disease. Some manifestation was present in 257. Their conclusions were stated as follows:

In the presence of severe anemia it is impossible to segregate dependably patients with primary cardiovascular involvement. All of the usual criteria of cardiovascular disease may occur solely as the result of anemia. These symptoms and findings are not restricted to any type of anemia or related to the severity of the anemia. Examination of the blood is essential for dependable differentiation. Cardiovascular manifestations often occur with hematologic decompensation and disappear after treatment or during a remission.

Paradoxical pulse, as measured by the sphygmomanometer, is seen in conditions other than constrictive pericarditis or pericardial tamponade. Osgood<sup>103</sup> observed that fluctuation as much as 30 mm of mercury systolic may occur in paroxysms of bronchial asthma with decline of the level during inspiration and rise during expiration. In some patients this fluctuation varied directly with the intensity of the asthmatic paroxysm. This phenomenon was explained by following and amplifying the observations of Reid,<sup>104</sup> who stated that the lungs are more important than is generally realized in promoting the return of blood to the left side of the heart.

102 Carter, J. B., and Traut, E. F. Cardiovascular Manifestations in Pernicious Anemia, *Arch Int Med* **72** 757 (Dec) 1943.

103 Osgood, H. Blood Pressure Fluctuations in Bronchial Asthma, *J Lab & Clin Med* **28** 927, 1943.

104 Reid, W. D. Respiration as a Factor in the Circulation of Blood, *Ann Int Med* **17** 206, 1942.

In this conception the flow of blood in the pulmonary veins is considered an active propulsion, as in the squeezing of a sponge, rather than an aspiration. The propulsion takes place during expiration. During inspiration the blood is held in the lung. This mechanism is exaggerated in asthma by the greater negative intrathoracic pressure during inspiration, which may result in a more pronounced dilatation of veins. It is also considered that the expiratory "squeeze" is perhaps greater because of increased thoracic pressure at that time.

In several patients observed at the Massachusetts General Hospital after the Cocoanut Grove catastrophe asthma developed as a result of severe bronchiolitis, which in turn resulted from the irritant gases inhaled.<sup>105</sup> A definite pulsus paradoxicus was observed in 3 cases, although this does not appear in the report.

Osgood and Ehret<sup>106</sup> extended their observations on changes in blood pressure in asthma, with special reference to the effect of therapeutic drugs. After injection of epinephrine hydrochloride the respiratory fluctuation approached normal when relief from the asthmatic attack was obtained. After intravenous injection of theophylline ethylenediamine there was a decrease in fluctuation, but of lesser magnitude. This difference in result suggested a possible difference in action of the two drugs. The authors suggest that the bronchodilating effect of theophylline ethylenediamine may be of secondary importance. Its principal action is thought to be an increase of blood flow through the pulmonary circuit by vasodilation.

105 Aub, J. C., Pittman, H., and Brues, A. M. Management of the Cocoanut Grove Burns at the Massachusetts General Hospital. The Pulmonary Complications, a Clinical Description, *Ann Surg* **117** 834, 1943.

106 Osgood, H., and Ehret, F. E. Blood Pressure Fluctuations in Bronchial Asthma, *J Lab & Clin Med* **28** 1415, 1943.

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